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Combined inhaled anticholinergics and short-acting beta$_2$-agonists for initial treatment of acute asthma in children (Review)

Griffiths B, Ducharme FM

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TABLE OF CONTENTS

ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
SUMMARY OF FINDINGS 3
BACKGROUND 4
OBJECTIVES 4
METHODS 4
RESULTS 6
Figure 1. 8
Figure 2. 10
Figure 3. 11
Figure 4. 12
DISCUSSION 14
AUTHORS' CONCLUSIONS 16
ACKNOWLEDGEMENTS 16
REFERENCES 17
CHARACTERISTICS OF STUDIES 21
DATA AND ANALYSES 63
Analysis 1.1. Comparison 1 Anticholinergic and beta2-agonists versus beta2-agonists alone (all protocols), Outcome 1 Primary outcome: hospital admissions. 66
Analysis 1.2. Comparison 1 Anticholinergic and beta2-agonists versus beta2-agonists alone (all protocols), Outcome 2 Primary outcome: hospital admissions subgrouped by trial protocol. 66
Analysis 1.3. Comparison 1 Anticholinergic and beta2-agonists versus beta2-agonists alone (all protocols), Outcome 3 Primary outcome: hospital admissions subgrouped by review authors' judgment of trial report. 67
Analysis 1.4. Comparison 1 Anticholinergic and beta2-agonists versus beta2-agonists alone (all protocols), Outcome 4 Primary outcome: hospital admissions subgrouped by control group event rate (tertiles). 69
Analysis 1.5. Comparison 1 Anticholinergic and beta2-agonists versus beta2-agonists alone (all protocols), Outcome 5 Primary outcome: hospital admissions subgrouped by co-intervention of corticosteroid. 70
Analysis 1.6. Comparison 1 Anticholinergic and beta2-agonists versus beta2-agonists alone (all protocols), Outcome 6 Change from baseline in % predicted FEV1, 60 minutes after the last of IB. 71
Analysis 1.7. Comparison 1 Anticholinergic and beta2-agonists versus beta2-agonists alone (all protocols), Outcome 7 Change from baseline in % predicted FEV1, 120 minutes after last IB. 71
Analysis 1.8. Comparison 1 Anticholinergic and beta2-agonists versus beta2-agonists alone (all protocols), Outcome 8 % Change in FEV1 or PEFR at 60 minutes after last IB (± 15 minutes). 72
Analysis 1.9. Comparison 1 Anticholinergic and beta2-agonists versus beta2-agonists alone (all protocols), Outcome 9 % Change in FEV1 or PEFR at 120 minutes after last IB (± 30 minutes). 72
Analysis 1.10. Comparison 1 Anticholinergic and beta2-agonists versus beta2-agonists alone (all protocols), Outcome 10 % Change in respiratory resistance at 60 minutes after IB (± 15 minutes). 72
Analysis 1.11. Comparison 1 Anticholinergic and beta2-agonists versus beta2-agonists alone (all protocols), Outcome 11 % Change in respiratory resistance at 120 minutes after IB (± 30 minutes). 73
Analysis 1.12. Comparison 1 Anticholinergic and beta2-agonists versus beta2-agonists alone (all protocols), Outcome 12 Change in clinical score at 120 minutes (± 30 minutes). 73
Analysis 1.13. Comparison 1 Anticholinergic and beta2-agonists versus beta2-agonists alone (all protocols), Outcome 13 Need for repeat bronchodilator treatment after standard protocol prior to disposition. 74
Analysis 1.14. Comparison 1 Anticholinergic and beta2-agonists versus beta2-agonists alone (all protocols), Outcome 14 O2 saturation < 95% at 60 minutes (± 15 minutes). 74
Analysis 1.15. Comparison 1 Anticholinergic and beta2-agonists versus beta2-agonists alone (all protocols), Outcome 15 O2 saturation < 95% at 120 minutes (± 30 minutes). 74
Analysis 1.16. Comparison 1 Anticholinergic and beta2-agonists versus beta2-agonists alone (all protocols), Outcome 16 Need for corticosteroids in emergency department prior to disposition. 75
Analysis 1.17. Comparison 1 Anticholinergic and beta2-agonists versus beta2-agonists alone (all protocols), Outcome 17 Tremor. 75
Analysis 1.18. Comparison 1 Anticholinergic and beta2-agonists versus beta2-agonists alone (all protocols), Outcome 18 Vomiting. 76

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Analysis 1.19. Comparison 1 Anticholinergic and beta2-agonists versus beta2-agonists alone (all protocols), Outcome 19 Nausea. 76
Analysis 1.20. Comparison 1 Anticholinergic and beta2-agonists versus beta2-agonists alone (all protocols), Outcome 20 Relapse. 76
ADDITIONAL TABLES 77
APPENDICES 81
WHAT'S NEW 81
HISTORY 81
CONTRIBUTIONS OF AUTHORS 82
DECLARATIONS OF INTEREST 82
SOURCES OF SUPPORT 82
DIFFERENCES BETWEEN PROTOCOL AND REVIEW 82
INDEX TERMS 82

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[Intervention Review]

Combined inhaled anticholinergics and short-acting beta$_2$-agonists for initial treatment of acute asthma in children

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ABSTRACT

Background

There are several treatment options for managing acute asthma exacerbations (sustained worsening of symptoms that do not subside with regular treatment and require a change in management). Guidelines advocate the use of inhaled short acting beta$_2$-agonists (SABAs) in children experiencing an asthma exacerbation. Anticholinergic agents, such as ipratropium bromide and atropine sulfate, have a slower onset of action and weaker bronchodilating effect, but may specifically relieve cholinergic bronchomotor tone and decrease mucosal edema and secretions. Therefore, the combination of inhaled anticholinergics with SABAs may yield enhanced and prolonged bronchodilation.

Objectives

To determine whether the addition of inhaled anticholinergics to SABAs provides clinical improvement and affects the incidence of adverse effects in children with acute asthma exacerbations.

Search methods

We searched MEDLINE (1966 to April 2000), EMBASE (1980 to April 2000), CINAHL (1982 to April 2000) and reference lists of studies of previous versions of this review. We also contacted drug manufacturers and trialists. For the 2012 review update, we undertook an 'all years' search of the Cochrane Airways Group's register on the 18 April 2012.

Selection criteria

Randomized parallel trials comparing the combination of inhaled anticholinergics and SABAs with SABAs alone in children (aged 18 months to 18 years) with an acute asthma exacerbation.

Data collection and analysis

Two review authors independently assessed trial quality and extracted data. We used the GRADE rating system to assess the quality of evidence for our primary outcome (hospital admission).

Main results

Twenty trials met the review eligibility criteria, generated 24 study comparisons and comprised 2697 randomised children aged one to 18 years, presenting predominantly with moderate or severe exacerbations. Most studies involved both preschool-aged children and school-aged children; three studies also included a small proportion of infants less than 18 months of age. Nine trials (45%) were at a low risk

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of bias. Most trials used a fixed-dose protocol of three doses of 250 mcg or two doses of 500 mcg of nebulized ipratropium bromide in combination with a SABA over 30 to 90 minutes while three trials used a single dose and two used a flexible-dose protocol according to the need for SABA.

The addition of an anticholinergic to a SABA significantly reduced the risk of hospital admission (risk ratio (RR) 0.73; 95% confidence interval (CI) 0.63 to 0.85; 15 studies, 2497 children, high-quality evidence). In the group receiving only SABAs, 23 out of 100 children with acute asthma were admitted to hospital compared with 17 (95% CI 15 to 20) out of 100 children treated with SABAs plus anticholinergics. This represents an overall number needed to treat for an additional beneficial outcome (NNTB) of 16 (95% CI 12 to 29).

Trends towards a greater effect with increased treatment intensity and with increased asthma severity were observed, but did not reach statistical significance. There was no effect modification due to concomitant use of oral corticosteroids and the effect of age could not be explored. However, exclusion of the one trial that included infants (< 18 months) and contributed data to the main outcome, did not affect the results. Statistically significant group differences favoring anticholinergic use were observed for lung function, clinical score at 120 minutes, oxygen saturation at 60 minutes, and the need for repeat use of bronchodilators prior to discharge from the emergency department. No significant group difference was seen in relapse rates.

Fewer children treated with anticholinergics plus SABA reported nausea and tremor compared with SABA alone; no significant group difference was observed for vomiting.

Authors' conclusions

Children with an asthma exacerbation experience a lower risk of admission to hospital if they are treated with the combination of inhaled SABAs plus anticholinergic versus SABA alone. They also experience a greater improvement in lung function and less risk of nausea and tremor. Within this group, the findings suggested, but did not prove, the possibility of an effect modification, where intensity of anticholinergic treatment and asthma severity, could be associated with greater benefit.

Further research is required to identify the characteristics of children that may benefit from anticholinergic use (e.g. age and asthma severity including mild exacerbation and impending respiratory failure) and the treatment modalities (dose, intensity, and duration) associated with most benefit from anticholinergic use better.

PLAIN LANGUAGE SUMMARY

Combined inhaled anticholinergics and beta$_2$-agonists for initial treatment of acute asthma in children

Background
In an asthma attack, the airways (small tubes in the lungs) narrow because of inflammation (swelling), muscle spasms and mucus secretions. Other symptoms include wheezing, coughing and chest tightness. This makes breathing difficult. Reliever inhalers typically contain short-acting beta$_2$-agonists (SABAs) that relax the muscles in the airways, opening the airways so that breathing is easier. Anticholinergic drugs work by opening the airways and decreasing mucus secretions.

Review question
We looked at randomised controlled trials to find out whether giving inhaled anticholinergics plus SABAs (instead of SABAs on their own) in the emergency department provides benefits or harms in children having an asthma attack.

Key results
We found that children with a moderate or severe asthma attack who were given both drugs in the emergency department were less likely to be admitted to the hospital than those who only had SABAs. In the group receiving only SABAs, on average 23 out of 100 children with acute asthma were admitted to hospital compared with an average of 17 (95% CI 15 to 20) out of 100 children treated with SABAs plus anticholinergics. Taking both drugs was also better at improving lung function. Taking both drugs did not seem to reduce the possibility of another asthma attack. Fewer children treated with anticholinergics reported nausea and tremor, but no significant group difference was observed for vomiting.

Quality of the evidence and further research
Most of the studies were in preschool- and school-aged children; three studies also included a small proportion of infants under 18 months of age, although there was no evidence that inclusion of these infants with wheezy episodes affected the results. Nine trials (45%) were at a low risk of bias and we regarded the evidence for hospitalisation as high quality. Physicians can administer the dose of anticholinergic and SABA in several different ways; as a single dose, or as a certain number of doses or more flexibly. Most of the trials gave the children two or three doses and we think that more research is needed to improve characterization of children that benefit from, and the most effective number and frequency of doses of, anticholinergic treatment.

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SUMMARY OF FINDINGS

Summary of findings for the main comparison. Anticholinergic and short-acting beta$_2$-agonists versus beta$_2$-agonists alone (all protocols) for initial treatment of acute asthma in children

Anticholinergic and shorth-acting beta$_2$-agonists (SABA) versus SABA alone (all protocols) for initial treatment of acute asthma in children

Patient or population: children with initial treatment of acute asthma
Settings: emergency department
Intervention: anticholinergic and SABA versus SABA alone (all protocols)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Anticholinergic and SABA versus SABA alone (all protocols)				
Primary outcome: hospital admissions hospital admissions	**23 per 100**	**17 per 100** (15 to 20)	**RR 0.73** (0.63 to 0.85)	2497 (19 studies)	⊕⊕⊕⊕ **high**	3 studies had no admissions so did not contribute to the RR.

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio; **SABA:** short-acting beta-agonists.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

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BACKGROUND

Description of the condition

Asthma is caused by inflammation in the airways and bronchoconstriction, which makes it difficult to breathe and leads to wheezing and breathlessness. The underlying inflammation causes the lining of the airways to secrete mucus, which also obstructs the free flow of air through the lungs. The bronchoconstriction is alleviated by using bronchodilators such as short acting beta$_2$-agonists (SABAs), while the underlying inflammation can be treated with regular inhaled corticosteroids. However, symptoms may flare up in response to an asthma trigger (e.g. virus, dust, pollen) leading to an asthma exacerbation. It is not known why the inflammation, secretions and bronchoconstriction occur. Asthma exacerbations can be life threatening and may require more medications than are used on a day-to-day basis.

Description of the intervention

The initial management of acute paediatric asthma exacerbations in children focuses on the rapid relief of bronchospasm using inhaled or nebulized bronchodilators (BTS 2011; GINA 2011). Children who do have moderate or severe asthma and those who do not respond sufficiently to bronchodilators to relieve symptoms require the addition of oral or intravenous glucocorticoids (BTS 2011; GINA 2011; Lougheed 2012). SABAs are clearly the most effective bronchodilators due to their rapid onset of action and the magnitude of achieved bronchodilation (Sears 1992; Svedmyr 1985; Teoh 2012). Anticholinergic agents, such as ipratropium bromide and atropine sulfate, have a slower onset of action and weaker bronchodilating effect, but may specifically relieve cholinergic bronchomotor tone and decrease mucosal edema and secretions (Chapman 1996; Gross 1988; Silverman 1990). Thus, the combination of inhaled anticholinergics with SABAs may yield enhanced and prolonged bronchodilation.

National and international guidelines recommend the addition of anticholinergics to inhaled SABAs in people with an acute severe asthma exacerbation and suggest consideration of this therapy in people with moderate exacerbations (BTS 2011; GINA 2011).

Why it is important to do this review

The first version of this Cochrane review published in 1997 found a significant reduction in hospital admissions in school-aged children with severe exacerbations receiving intensive anticholinergic treatment. The review was updated in 2000 with the addition of three new trials further strengthening the initial conclusions (Plotnick 2000). With the identification of seven new studies, the 2012 update aims to examine the conclusions of the earlier version of this review and explore if characteristics of participants or treatment are associated with increased benefit.

OBJECTIVES

To determine whether the addition of inhaled anticholinergics to inhaled SABAs provides clinical improvement and affects the incidence of adverse effects in children with acute asthma exacerbations.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) conducted in an emergency department setting, comparing the combination of an inhaled anticholinergic drug and SABA versus a SABA alone in the treatment of an acute asthma exacerbation.

Types of participants

Children aged 18 months to 18 years presenting to an emergency department with an acute exacerbation of asthma. Where studies included children younger than 18 months, we excluded them if the younger children contributed more than 5% of the total study population (post-hoc decision).

Types of interventions

Treatment group: single or repeated doses of nebulized or inhaled short-acting anticholinergics plus SABAs.

Control group: single or repeated doses of nebulized or inhaled placebo plus SABAs.

Types of outcome measures

Primary outcomes

Hospital admission.

Secondary outcomes

1. Change from baseline in % predicted forced expiratory volume in one second (FEV_1) (60 and 120 minutes after the last combined anticholinergic and SABA inhalation).
2. Percent change from baseline in FEV_1 (60 and 120 minutes after the last combined inhalation).
3. Change from baseline in respiratory resistance (60 and 120 minutes after the last combined inhalation).
4. Change from baseline in clinical score (60 and 120 minutes after the last combined inhalation).
5. Oxygen saturation (60 and 120 minutes after the last combined inhalation).
6. Need for repeated bronchodilator treatments after the intervention/placebo protocol, prior to disposition.
7. Need for systemic corticosteroids.
8. Adverse effects such as nausea, vomiting and tremor.
9. Relapse rate.

Search methods for identification of studies

Electronic searches

For the previous version of this review, MEDLINE (1966 to April 2000), EMBASE (1980 to April 2000) and CINAHL (1982 to April 2000) were searched using the following MeSH, full text and keyword terms: [asthma, wheez* or respiratory sounds] and [random*, trial*, placebo*, comparative study, controlled study, double-blind, single-blind] and [child* or infan* or adolescen* or pediatr* or paediatr*] and [emergenc* or acute*] and [ipratropium* or anticholinerg* or atropin*].

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For the 2012 review update, we undertook an 'all years' search of the Cochrane Airways Group Register of Trials with the following terms: anticholinergic* or anti-cholinergic* or atropine* or ipratropium or tiotropium or oxitropium or Aclidinium) AND ((beta* and agonist) or bronchodilat* or salbutamol or fenoterol or albuterol or terbutaline or metaproterenol) and (child* or paediat* or pediat* or adolesc* or infan* or toddler* or bab* or young* or preschool* or "pre school*" or pre-school* or newborn* or "new born*" or new-born* or neo-nat* or neonat*.

Searching other resources

We reviewed bibliographies of all trials and review articles identified through searches to identify potentially relevant citations. We contacted the manufacturer of ipratropium bromide, Boehringer Ingelheim, for the original review and the update, to identify other published or unpublished trials. We contacted trialists working in the field of paediatric asthma to identify potentially relevant trials.

Data collection and analysis

Selection of studies

In the updated search, one review author (BG) examined each new citation (title and abstract) identified through one of the above strategies and classified as clearly included, possibly included or clearly not an RCT. We retrieved and assessed full-text articles of all citations identified as definite or possible RCTs, irrespective of language of publication. BG and Toby Lasserson (former Managing Editor of the Cochrane Airways Group) assessed the full text independently to determine if the study met the inclusion criteria. We resolved any disagreement by consensus. Emma Welsh (Managing Editor of the Cochrane Airways Group) and Elizabeth Stovold (Trials Search Co-ordinator of the Cochrane Airways Group) assisted in screening repeat literature searches prior to publication.

Data extraction and management

Two review authors independently extracted data from eligible studies and entered data into the Characteristics of included studies table.

Assessment of risk of bias in included studies

One review author (BG) and one member of the Cochrane Airways Group (TL or EJW) assessed the risk of bias. Agreement was reached independently in each case. We assessed the risk of bias as high, low or unclear in accordance with recommendation in the *Cochrane Handbook for Systematic Reviews of Interventions* for the following domains (Higgins 2011):

1. random sequence generation (selection bias);
2. allocation concealment (selection bias);
3. blinding (performance bias and detection bias);
4. incomplete outcome data (attrition bias);
5. selective reporting (reporting bias);
6. other bias.

Measures of treatment effect

We analyzed treatment effects for dichotomous outcomes as pooled risk ratios (RR). For continuous outcomes, we used the mean difference (MD) or the standardized mean difference (SMD) to estimate the pooled effect size. For example, the MD was reported for pulmonary function tests using the same unit of measure. We used the SMD, reported in 'standard deviation units', when the change in the same pulmonary function test was reported in different units (change in % predicted FEV_1 and % change in FEV_1). We presented pooled effect sizes along with the 95% confidence intervals (CI).

Dealing with missing data

We attempted to contact the study investigators or study sponsors to verify study methodology and extracted information and to provide additional data if necessary.

Assessment of heterogeneity

We used the I^2 statistic for assessing the level of statistical heterogeneity between the results of the studies. We used the following levels of I^2 as a guide:

- 0% to 40% may not be important;
- 30% to 60% may represent moderate heterogeneity;
- 50% to 90% may represent substantial heterogeneity;
- 75% to 100% considerable heterogeneity.

Assessment of reporting biases

We visually inspected funnel plot symmetry where we had more than 10 trials contributing data to a meta-analysis in an effort to detect possible biases.

Data synthesis

We entered data into Review Manager 5.1 software (RevMan 2011). Treatment effects for dichotomous outcomes were analyzed and reported as pooled RRs using the fixed-effect model (Greenland 1985), or, in case of substantial, unexplained heterogeneity, the random-effects model (DerSimonian 1986).

Subgroup analysis and investigation of heterogeneity

We postulated a priori that three factors may potentially influence the magnitude or direction, or both, of the therapeutic response, namely:

1. the intensity of anticholinergic treatment;
2. co-intervention with glucocorticoids; and
3. the severity of exacerbation (based on documented/reported severity by authors and by tertile of admission rate).

Therefore, RCTs were grouped according to the intensity of anticholinergic protocol (single-dose regimen, multiple fixed-dose regimen, multiple flexible-dose regimen) and stratified on the presence/absence of systemic glucocorticoids. Whenever reported, the baseline % predicted FEV_1 and hospital admission rate in the control groups were recorded as indicators of severity and examined for their potential interaction with therapeutic effect.

In order to evaluate the effect of baseline severity on the magnitude of response to the intervention, we stratified trials according to severity documented or reported by authors as per the original review. In addition, we ranked each study in increasing order of the control group admission rate as a proxy for severity. We then split these arbitrarily into tertiles, which we referred to as low, medium or high risk. If the admission rate for a particular study was not available, we did not rank that study.

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For the 2012 update, we considered adding a subgroup analysis by age of child; however, the overlap in age ranges included in each study precluded this analysis. We considered also doing a subgroup analysis based on cumulative dose of ipratropium delivered. However, this analysis was potentially confounded by the severity of the asthma exacerbation of the children included in the trials as well as differences between the drug delivery methods (nebulizers versus metered-dose inhalers (MDI) and spacers) and was thus omitted.

Sensitivity analysis

We performed sensitivity analyses to examine the effect on results of excluding unpublished trials, those with poor methodological quality and studies that included a small proportion of children under 18 months of age (less than 5% of total study participants).

RESULTS

Description of studies

Results of the search

For the 2012 update, the search retrieved 223 references for screening (18 April 2012). We excluded studies that had already been assessed for inclusion in the first version of the review and obtained 19 citations for full-text scrutiny. These citations referred to 19 studies (see Appendix 1 for details of previous search results) and seven new trials met the eligibility criteria for inclusion.

Included studies

Trial protocol/dose regimen

Overall, there were 20 included trials and three trials generated additional comparisons. Two studies provided stratified data subgrouped by severity (Qureshi 1998; Zorc 1999), and one study evaluated two different dosing strategies against control (Schuh 1995). Overall, there were 24 comparisons. We subgrouped trials according to the intensity of the anticholinergic protocol (see Table 1). Six trials on 570 children tested a single dose of ipratropium bromide added to multiple (two to six) doses of SABAs given every 20 to 30 minutes. We termed these the 'single-dose protocol'.

In 16 intervention arms with 2191 children, doses of ipratropium bromide were administered at multiple fixed time points after the trial began. We termed these trials 'multiple fixed-dose protocol'. The doses of ipratropium bromide varied from 120 mcg to 500 mcg and the number of doses ranged between two and six over 30 to 90 minutes.

Two studies including 84 children added a dose of anticholinergic to every SABA, leaving the number of inhalations determined by the child's need. These were termed 'multiple flexible-dose protocol'. Calvo 1998 used a fixed dose of ipratropium bromide (20 mcg) given up to seven times in two hours. Treatment was stopped after the child's clinical score dropped below a predetermined threshold. Guill 1987 used a fixed dose of atropine sulfate (0.05 to 0.1 mg/kg) up to three times at 20-minute intervals. Treatment was continued until symptoms were controlled or the subject was admitted to hospital.

With one exception that used atropine (Guill 1987), ipratropium bromide was used as the anticholinergic agent.

Participants

Three studies with children younger than 18 months were included (Benito Fernandez 2000; Guill 1987; Phanichyakam 1990). Only Benito Fernandez 2000 reported data for the primary outcome and we tested whether inclusion of this study would unduly affect the analysis (although unlikely, as the mean age of children in the study was 5.7 years).

Outcomes

The most frequently reported outcomes were hospital admission rate and spirometric measurements. Nineteen intervention arms (from 16 studies) reported our primary outcome of hospital admission rate. Of note, 84% of the weight in this outcome was contributed by trials focusing on children with documented or reported moderate or severe airway obstruction and 87% of the weight was contributed by trials in the higher and middle tertile of admission rate. Not all trials considered each outcome. The reporting of adverse and side effects was variable. Adverse effects such as hypertension or tachycardia were reported so infrequently that they could not be considered in this review. Whenever reported, we extracted side effects such as nausea, vomiting and tremor, which may interfere with children's compliance. All reported outcomes are listed in the Characteristics of included studies table.

Defining severity using admission rate

No single baseline spirometric characteristic was consistently reported across all studies. Hence insufficient lung function data were provided to enable us to determine the asthma severity of children at the start of trials. We ascertained asthma severity in two ways.

First, as per the original protocol, we stratified severity using lung function or clinical score at baseline and used both the eligibility/exclusion criteria and the severity reported by authors to confirm our assessment (see Table 2).

Eight studies were judged as 'severe' (Benito Fernandez 2000; BI [pers comm]; Qureshi 1997; Qureshi 1998 (severe); Reisman 1988; Schuh 1995 (multiple); Sharma 2004; Zorc 1999 (severe)), four studies as 'moderate and severe' (Iramain 2011; Peterson 1996; Watanasomsiri 2006; Watson 1988), three studies as moderate (Calvo 1998; Qureshi 1998 (moderate); Zorc 1999 (moderate)), two studie as 'mild and moderate ' (Chakraborti 2006; Ducharme 1998), and one study as 'mild' (Zorc 1999 (mild)) asthma.

Sienra Monge 2000 did not provide enough information to confirm the authors' judgment and was left unrated (it did not provide data for the primary outcome).

Next, we used the control group event rate as a proxy for severity. Studies were ranked by the order of the admission rate of the control group, and divided into three groups and labelled as high, medium and low admission rates (see Table 3).

Ranking of severity based on admission rate in the control group corresponded somewhat but not perfectly to ranking based on mean baseline % predicted FEV_1 in the studies that reported it or authors' reports. Ranking on admission rate permitted the inclusion of studies that did not use spirometry or did not report

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mean baseline % predicted FEV_1. The ranking admission rate varied from 0 to 0.53.

Studies from the multiple dose-fixed and single-dose protocols provided hospital admission data and were, therefore, ranked in this manner.

We define six intervention arms from 'multiple dose-fixed protocol' trials as a high admission rate (Benito Fernandez 2000; Iramain 2011; Qureshi 1997; Qureshi 1998 (severe); Schuh 1995 (multiple); Schuh 1995 (single)), six as medium admission rate (Ducharme 1998; Peterson 1996; Reisman 1988; Sharma 2004; Zorc 1999 (moderate); Zorc 1999 (severe)), and six as low admission rate (BI [pers comm]; Chakraborti 2006; Qureshi 1998 (moderate); Watanasomsiri 2006; Watson 1988; Zorc 1999 (mild)). We were unable to rank six studies because admission rates were not provided (Beck 1985; Calvo 1998; Cook 1985; Guill 1987; Phanichyakam 1990; Sienra Monge 2000).

Excluded studies

We excluded 30 studies; common reasons for exclusion of studies were: studies on people with chronic or stable asthma (N = 13), hospitalised people (N = 6), inappropriate protocols (e.g. different SABAs in each arm or SABAs at different doses) (N = 4), adults (N = 3), infants (N = 2), non-randomized control trials (N = 2) and conference abstracts (N = 2). Full details are given in the Characteristics of excluded studies table.

Risk of bias in included studies

The judgment for each risk of bias domain for each study is included in the Characteristics of included studies table and an overview is given in Figure 1. Methodology of nine of the 19 trials was confirmed by the authors (Calvo 1998; Cook 1985; Ducharme 1998; Guill 1987; Peterson 1996; Qureshi 1997; Qureshi 1998 (severe); Schuh 1995; Zorc 1999 (moderate)).

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Figure 1. Methodological quality summary: review authors' judgments about each methodological quality item for each included study.

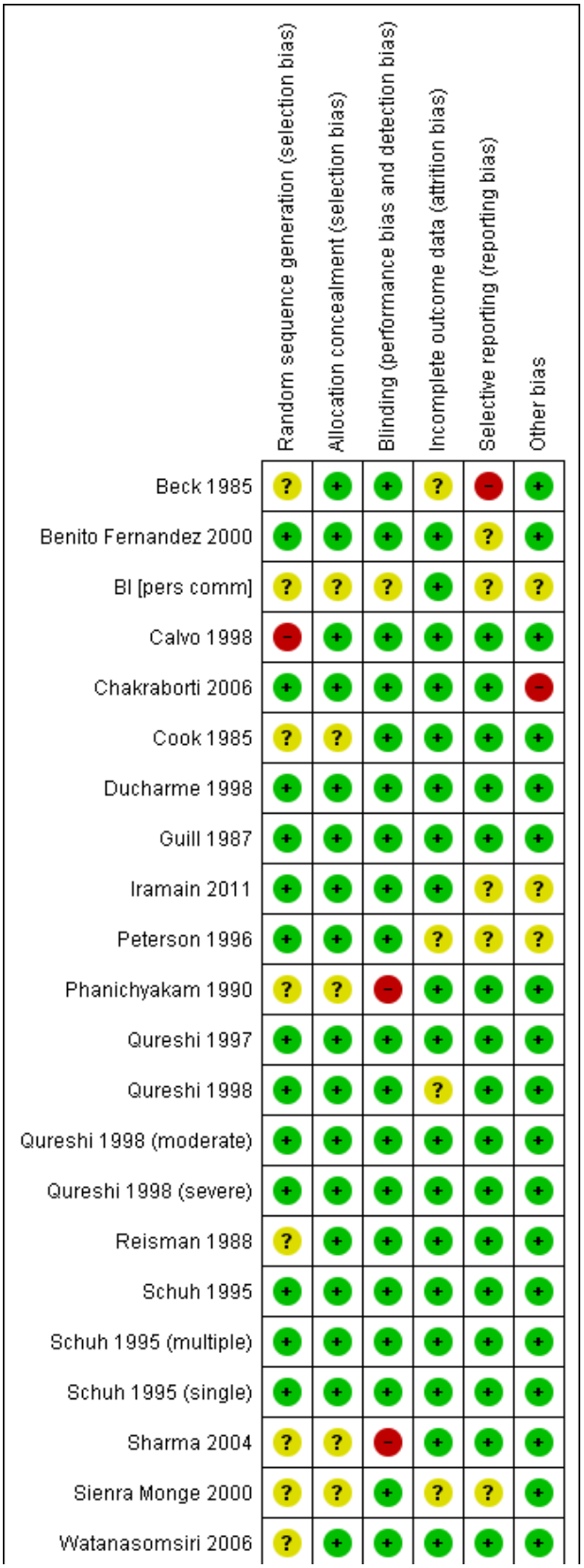

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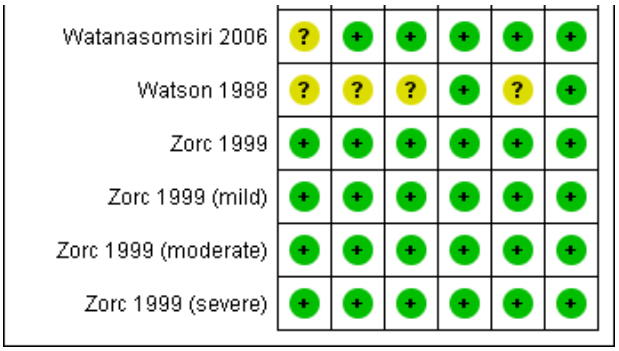
Figure 1. (Continued)



Allocation

We considered 10 studies to be at low risk of selection bias: randomisation was performed using computer-generated random numbers in six studies (Chakraborti 2006; Ducharme 1998; Guill 1987; Iramain 2011; Peterson 1996; Zorc 1999 (mild)), tables of random numbers in three trials (Qureshi 1997; Qureshi 1998; Schuh 1995 (multiple); Schuh 1995 (single)), and one trial used block randomisation (Benito Fernandez 2000). Nine studies did not describe the method of randomisation and were classified as unclear risk of bias, one study used consecutive assignment and was judged to be at high risk of bias (Calvo 1998).

We considered 14 trials to be at low risk of bias for allocation concealment; 12 studies used number-coded solutions supplied by the pharmacy (Beck 1985; Benito Fernandez 2000; Calvo 1998; Ducharme 1998; Iramain 2011; Peterson 1996; Qureshi 1997; Qureshi 1998 (moderate); Reisman 1988; Schuh 1995 (single); Watanasomsiri 2006; Zorc 1999 (mild)), one study used opaque consecutive numbered envelopes containing assignment (Guill 1987), and one study "used a person not involved in the study" (Chakraborti 2006). Allocation concealment was at unclear risk of bias in the remaining six studies.

Blinding

Sixteen studies claimed double-blinding while two were described as triple-blind (Ducharme 1998; Peterson 1996), and two were unblinded (Phanichyakam 1990; Sharma 2004). Twelve studies used an identical placebo in the control group, one study described a similarly looking intervention and placebo solutions (Cook 1985), and three studies did not provide details of the blinding method (BI [pers comm]; Sienra Monge 2000; Watson 1988). It was assumed that the person making the decision to admit to hospital was also blinded to the medication received but only one study described them as blinded (Schuh 1995).

Incomplete outcome data

Thirteen studies reported the presence/absence of participant withdrawal or dropout and the reasons for the attrition if applicable (BI [pers comm]; Calvo 1998; Cook 1985; Ducharme 1998; Guill 1987; Iramain 2011; Peterson 1996; Qureshi 1997; Qureshi 1998 (moderate); Schuh 1995; Watanasomsiri 2006; Watson 1988; Zorc 1999 (severe)). One study referred to 40 children in the abstract but presented data for only 30 children with no clear explanation (Sienra Monge 2000).

Selective reporting

One study recorded data for hospital admission but did not publish the data and commented that the "hospital admission data was not significant" (Beck 1985).

Effects of interventions

See: **Summary of findings for the main comparison** Anticholinergic and short-acting beta$_2$-agonists versus beta$_2$-agonists alone (all protocols) for initial treatment of acute asthma in children

First we present the primary outcome with all protocols, then we present the prespecified subgroup analyses (trial protocol, severity, co-intervention of corticosteroid) followed by the secondary outcomes. We did not subgroup the secondary outcomes.

Primary outcome: admission to hospital

When anticholinergics were delivered in addition to SABAs, there was a significant decrease in the risk of hospital admission versus SABAs and placebo (RR 0.73; 95% CI 0.63 to 0.85; Figure 2). The primary analysis was inclusive of all study protocols (single dose, multiple-fixed and multiple-flexible); however, only studies using single and multiple-fixed dose protocols reported data for this outcome. Fifteen studies (nineteen comparisons) reported data for this outcome, but the absence of admission in three studies mean that the pooled RR was based on data from 16 comparisons (2326 children). The result was statistically significant (P value < 0.0001) and there was no evidence of statistical heterogeneity between the study results (I^2 = 0%). In the children receiving SABAs only, 23 people out of 100 were admitted to hospital compared with 17 (95% CI 15 to 20) out of 100 for children receiving SABAs plus anticholinergics (Figure 3). This represents an overall number needed to treat for an additional beneficial effect (NNTB) of 16 (95% CI 12 to 29).

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Figure 2. Forest plot of comparison: 1 Anticholinergic and short-acting beta$_2$-agonists versus short-acting beta$_2$-agonists alone (all protocols), outcome: 1.1 Primary outcome: hospital admissions.

Study or Subgroup	Anticholinergic + SABA Events	Total	SABA Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Benito Fernandez 2000	18	51	27	51	9.3%	0.67 [0.42, 1.05]
BI [pers comm]	19	246	23	254	7.8%	0.85 [0.48, 1.53]
Calvo 1998	0	40	0	40		Not estimable
Chakraborti 2006	0	30	0	30		Not estimable
Ducharme 1998	23	156	24	142	8.6%	0.87 [0.52, 1.47]
Iramain 2011	9	53	21	53	7.2%	0.43 [0.22, 0.85]
Peterson 1996	19	82	25	81	8.7%	0.75 [0.45, 1.25]
Qureshi 1997	9	36	14	31	5.2%	0.55 [0.28, 1.10]
Qureshi 1998 (moderate)	8	91	9	98	3.0%	0.96 [0.39, 2.37]
Qureshi 1998 (severe)	51	137	71	136	24.5%	0.71 [0.54, 0.93]
Reisman 1988	2	11	3	13	0.9%	0.79 [0.16, 3.90]
Schuh 1995 (multiple)	17	40	9	20	4.1%	0.94 [0.52, 1.73]
Schuh 1995 (single)	15	40	10	21	4.5%	0.79 [0.43, 1.44]
Sharma 2004	1	25	4	25	1.4%	0.25 [0.03, 2.08]
Watanasomsiri 2006	2	38	3	33	1.1%	0.58 [0.10, 3.26]
Watson 1988	0	16	0	15		Not estimable
Zorc 1999 (mild)	6	60	4	57	1.4%	1.43 [0.42, 4.79]
Zorc 1999 (moderate)	18	98	25	96	8.7%	0.71 [0.41, 1.21]
Zorc 1999 (severe)	7	22	12	29	3.6%	0.77 [0.36, 1.63]
Total (95% CI)		**1272**		**1225**	**100.0%**	**0.73 [0.63, 0.85]**
Total events	224		284			

Heterogeneity: Chi² = 7.25, df = 15 (P = 0.95); I² = 0%
Test for overall effect: Z = 4.13 (P < 0.0001)

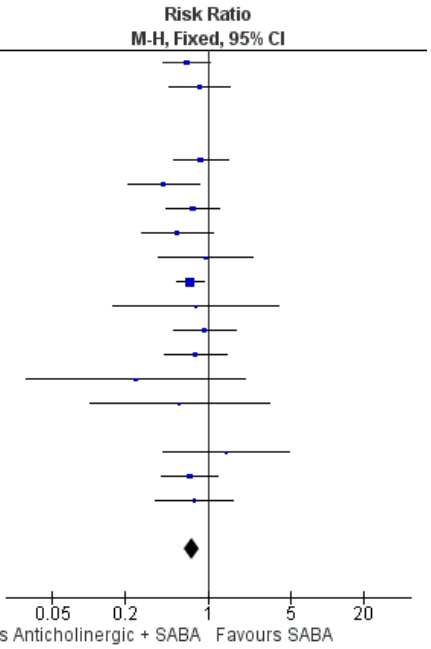

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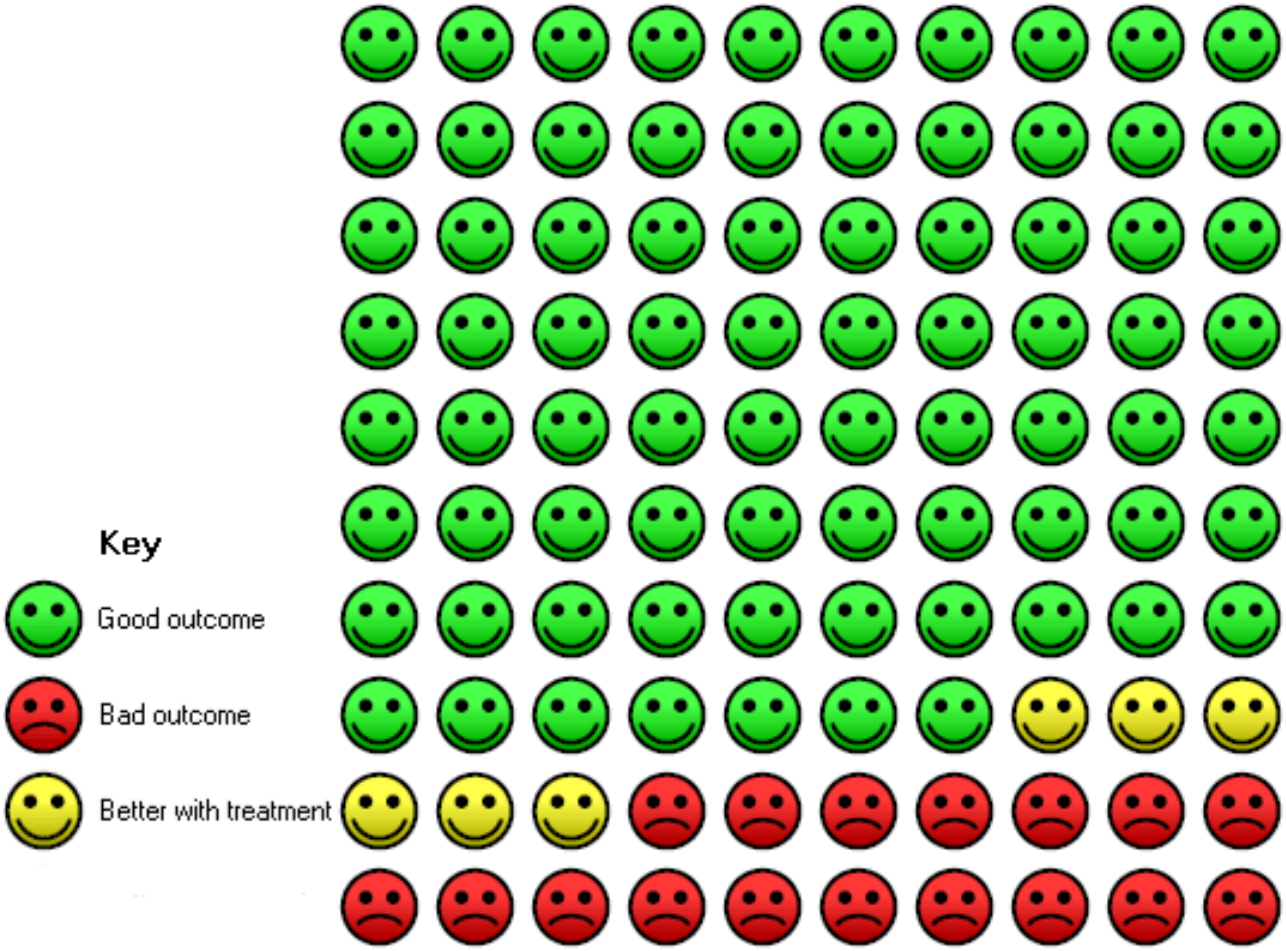
Figure 3. In the children on short-acting beta$_2$-agonists only, 23 people out of 100 were admitted to hospital, compared with 17 (95% CI 15 to 20) out of 100 for children on short-acting beta$_2$-agonists plus anticholinergics.



A funnel plot of the results for this outcome did not appear to indicate obvious signs of publication bias (Figure 4).

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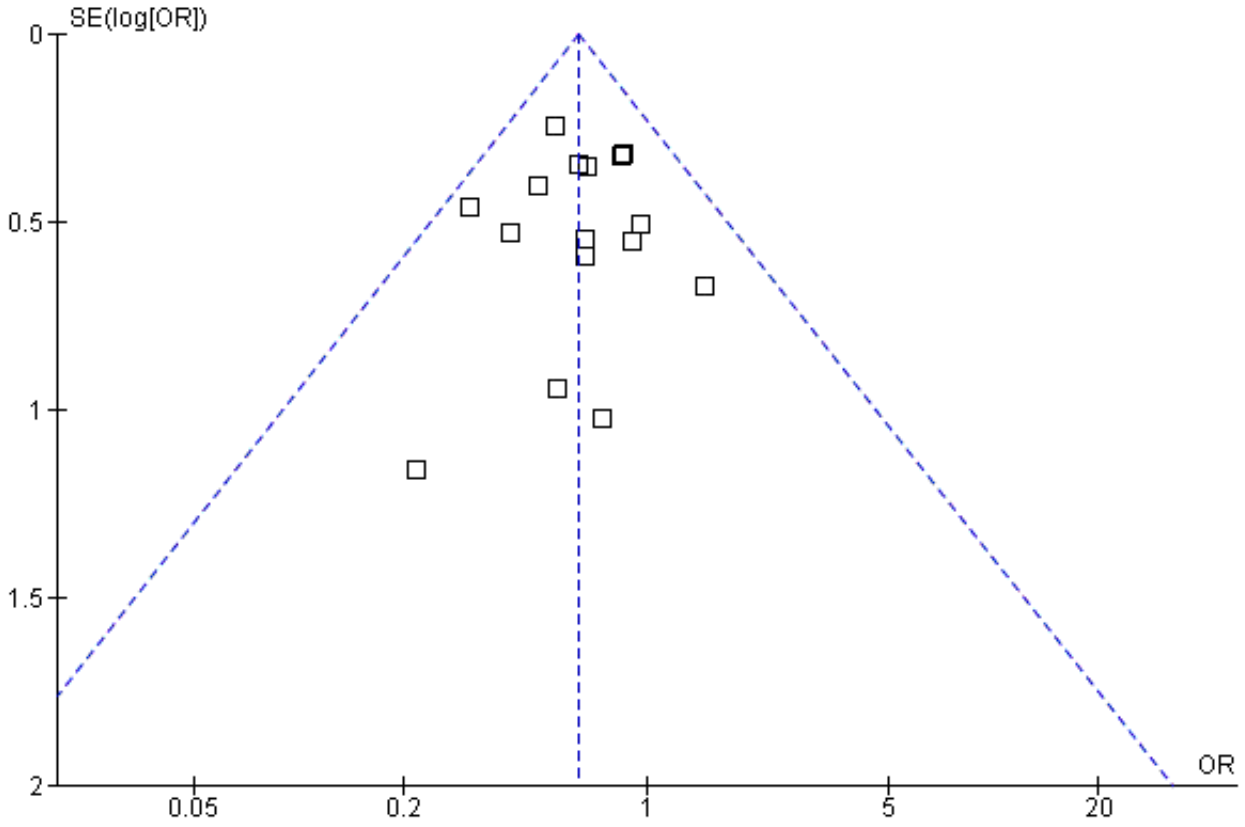
Figure 4. Funnel plot of analysis 1.1.



Primary outcome: admission to hospital: subgroup analysis by study protocol

Subgrouping the studies by study protocol for the same outcome showed no statistically significant difference between subgroups (test for subgroup differences: Chi^2 = 0.55, degrees of freedom (df) = 1, P value = 0.46, I^2 = 0%), although the power was low due to marked group imbalances in weight (Analysis 1.2). Fifteen intervention arms including 1998 children were subgrouped into the multiple fixed-dose protocol group. Of interest, anticholinergics delivered as a multiple fixed-dose regimen in 11 studies on 1998 children led to a decrease in the risk of hospital admission by 28% compared with SABA alone (RR 0.72; 95% CI 0.61 to 0.84). This result was statistically significant (P value < 0.0001) with no evidence of heterogeneity (I^2 = 0%). However, pooling data from only three studies (including 419 children) that used a single-dose regimen showed no significant reduction in risk (RR 0.84; 95% CI 0.56 to 1.26). Studies grouped into the multiple flexible-dose protocol did not provide data for this outcome. Due to subgroup imbalance in number and severity, we cannot firmly conclude on whether the intensity of therapy makes a difference in the magnitude of effect of treatment.

Primary outcome: admission to hospital: subgroup analysis by author's judgment of asthma severity and control group admission rate (multiple dose - fixed protocol)

Efforts had been made in previous versions of this review to stratify studies by asthma severity based on baseline lung function or clinical score and validated by both the eligibility and exclusion criteria and the authors' assessment of severity (Table 2). The studies were classified as severe, moderate and severe, moderate, mild and moderate, and mild. There was no significant difference between the RRs in these severity subgroups (test for subgroup differences: Chi^2 = 2.58, df = 4, P value = 0.63, I^2 = 0%; Analysis 1.3). Admittedly, the number of subgroups may have decreased the power to detect statistically significant subgroup differences.

In the eight studies including 1188 children, judged as experiencing a severe asthma exacerbation, a 27% decrease in the risk of admission (RR 0.73; 95% CI 0.61 to 0.87) was observed with anticholinergic treatment.

In the four studies including 371 children, rated as having a moderate or severe asthma exacerbation, a 40% reduction in risk of hospitalisation (RR 0.60; 95% CI 0.41 to 0.89) was documented in favor of anticholinergic treatment. In the three studies with 463 children experiencing a moderate asthma exacerbation, no significant reduction in risk of hospitalisation (RR 0.77; 95% 0.49 to 1.22) was observed although the effect size was of similar magnitude to that in the preceding groups.

Two studies including 358 children experiencing mild and moderate asthma exacerbations showed a non-significant reduction in hospital admission (RR 0.87; 95% CI 0.52 to 1.47).

In 117 children judged as experiencing a mild asthma exacerbation, there was no apparent beneficial effect on hospital admission with a wide confidence interval (RR 1.43; 95% CI 0.42 to 4.79).

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In this review update, we subgrouped hospital admissions using our proxy measure for severity derived from the control group event rate for hospitalisation (see Table 3). The studies were grouped into tertiles corresponding to high, medium and low risk of admission (high risk, admission rate ≥ 43%; medium risk, admission rate 10% to 42%; and low risk < 10%). There was no significant difference between the RRs in the severity subgroups (test for subgroup differences: $Chi^2 = 1.68$, df = 2, P value = 0.43, $I^2 = 0\%$).

Six studies on 669 children were grouped in the upper tertile with the highest control group admission rates: there was a 32% decrease in the risk of admission with the use of anticholinergics (RR 0.68; 95% CI 0.56 to 0.82; Analysis 1.4). In the six studies on 780 children in the medium-risk group, the use of anticholinergics reduced the risk of admission by 25% (RR 0.75; 95% CI 0.57 to 0.99). In the subgroup with the lowest control group event rates that included six studies on 968 children, the use of anticholinergics did not significantly reduce the risk of hospital admission (RR 0.91; 95% CI 0.59 to 1.42). Comparing the control group weighted risk against the treatment group's risk, the NNTB in the high-risk group was 7 (95% CI 5 to 12) versus 17 (95% CI 10 to 415) in the medium-risk group and 139 (not statistically significant) in the low-risk group (see Table 4).

Irrespective of the methods to classify severity, the findings would suggest that, within this group of trials of children with predominantly moderate and severe asthma, those with the most severe airway obstruction and a baseline risk of admission of more than 40% showed the largest numerical benefit from the addition of anticholinergics, with an intermediate effect in those with moderate airway obstruction or a baseline risk of admission between 10% and 40% and no significant effect in the few trials pertaining only to children with mild asthma.

Primary outcome: admission to hospital: subgroup analysis by co-intervention with corticosteroids

Studies were grouped by co-intervention with corticosteroids (Analysis 1.5). There was no significant difference between the subgroups (test for subgroup differences: $Chi^2 = 0.66$, df = 3, P value = 0.88, $I^2 = 0\%$). In the eight studies that administered corticosteroids to all children, the addition of an anticholinergic showed a reduction in the risk of hospital admission (RR 0.71; 95% CI 0.59 to 0.86). In the six studies that did not give corticosteroids to all children, the addition of an anticholinergic showed a significant reduction in risk (RR 0.67; 95% CI 0.47 to 0.94). In the three studies that administered corticosteroids at the physician's discretion, the point estimate was similar, but the confidence interval crossed unity (RR 0.77; 95% CI 0.54 to 1.10). This subgroup analysis would suggest that the effect of an anticholinergic was present, independently from the administration of systemic corticosteroids.

Secondary outcomes: lung function

Five studies on 402 children reported data for change in % predicted FEV_1 across two study protocols (single- and multiple-dose protocols) (Analysis 1.6). Children treated with an anticholinergic showed a significant improvement from baseline in % predicted FEV_1 at 60 minutes compared to those treated with SABA alone (MD 10.08; 95% CI 6.24 to 13.92). Two studies on 117 children reported data for the same outcome at 120 minutes (Analysis 1.7), which also showed a statistically significant improvement in % predicted FEV_1 in the treatment group versus the control group (MD 6.87; 95% CI 1.17 to 12.56). Fewer studies provided data for change in absolute FEV_1 or in peak expiratory flow rate (PEFR) at 60 minutes (Analysis 1.8) or 120 minutes (Analysis 1.9); although in both cases appeared to favor the use of salbutamol plus an anticholinergic over salbutamol alone, it was only statistically significant at 60 minutes (SMD 0.57; 95% CI 0.25 to 0.88).

Secondary outcome: respiratory resistance

In a post hoc analysis of one trial examining 294 children with mild to moderate exacerbations, stratified on concurrent use of systemic corticosteroids, no statistically significant group difference in respiratory resistance observed at 60 minutes (Analysis 1.10) and at 120 minutes (Analysis 1.11) suggesting no significant influence of concurrent corticosteroids on the magnitude of effect associated with a single dose of ipratropium bromide (Ducharme 1998).

Secondary outcome: change in clinical score

No studies provided data on clinical score at 60 minutes; however, three studies on 934 children provided data for clinical score at 120 minutes. Of these three studies, only two included means with standard deviations. Combining these two results showed that subjects treated with an anticholinergic had a greater improvement in clinical score at 120 minutes (SMD -0.23; 95% CI -0.42 to -0.04; Analysis 1.12).

Secondary outcome: oxygen (O_2) saturation at 60 minutes post therapy

In two trials reporting data for oxygen saturation there was a significant group difference at 60 minutes (RR 0.73; 95% CI 0.55 to 0.97; 415 children; Analysis 1.14), but not at 120 minutes (RR 1.10; 95% CI 0.76 to 1.59; 185 children; Analysis 1.15).

Secondary outcome: need for repeat bronchodilator treatment required after standard protocol prior to disposition

Nine studies on 1074 children reported data for the number of children who required repeat treatments of bronchodilator after the study protocol finished and before discharge. Subjects treated with the anticholinergic protocol were 13% less likely to require a repeat bronchodilator treatment before discharge (RR 0.87; 95% CI 0.79 to 0.97; Analysis 1.13).

Secondary outcome: adverse events (tremor, vomiting and nausea)

Adverse events reported included tremor, vomiting and nausea. Analysis of nine studies on 524 children showed that children treated with the addition of an anticholinergic were significantly less likely to experience tremor than those treated with inhaled SABAs alone (RR 0.69; 95% CI 0.51 to 0.93; Analysis 1.17). Similarly, analysis of seven studies including 757 children showed that children treated with an anticholinergic were significantly less likely to suffer from nausea (RR 0.60; 95% CI 0.38 to 0.95; Analysis 1.19). Analysis of eight studies on 1230 children observed no statistically significant group difference on vomiting (RR 0.88; 95% CI 0.49 to 1.56; Analysis 1.18).

Secondary outcome: relapse

Ten studies on 1389 children reported the relapse rate of children initially discharged from the emergency department during the follow-up period. No statistically significant difference between groups was observed (RR 1.07; 95% CI 0.68 to 1.68; Analysis 1.20).

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Sensitivity analysis

Three sensitivity analyses were performed to examine the impact of unpublished data, the inclusion of studies with very young children and inclusion of trials with lower reported methodological quality.

Excluding the two unpublished studies (BI [pers comm]; Peterson 1996) from the primary outcome (all treatment protocols) did not alter the direction or significance level of the risk of admission (RR 0.72; 95% CI 0.61 to 0.84).

Of the three included studies that included children under 18 months of age (Benito Fernandez 2000; Guill 1987; Phanichyakam 1990), only Benito Fernandez 2000 contributed data to the primary outcome. Removing this study from the primary outcome (all treatment protocols) made very little difference to the overall result and no impact on the statistical significance (RR 0.74; 95% CI 0.63 to 0.86).

Excluding the five studies (Beck 1985; Calvo 1998; Chakraborti 2006; Phanichyakam 1990; Sharma 2004) with lower reported methodological quality and thus at higher risk of bias also did not alter the direction or significance level of the result (RR 0.74; 95% CI 0.64 to 0.86).

DISCUSSION

Summary of main results

Primary outcome: hospital admissions

In children with predominantly moderate and severe asthma exacerbation, the combination of an anticholinergic and SABA significantly reduced the risk of hospital admission, the primary outcome of this review. This result was derived from 15 studies (19 comparisons) and 2497 children. Does this result alone justify the use of an anticholinergic in the treatment of all children with acute asthma? To investigate this further we performed several subgroup analyses and considered the validity of these results and their significance for practice.

Different treatment protocols used in the trials

An anticholinergic was administered as a single dose, multiple doses according to a fixed protocol, or a flexible dosing regimen where the an anticholinergic was systematically added to every SABA treatment until sufficient clinical improvement for discharge. This fundamental difference in treatment protocols prompted the first subgroup analysis by study protocol. The majority of data came from trials using multiple doses of ipratropium added to inhaled SABA with a fixed protocol: these trials used doses between 250 mcg and 500 mcg usually via a nebulizer device, with all but one using two or three doses over 30 to 90 minutes. There was a 28% statistically significant reduction in the risk of hospital admission in favor of anticholinergics. The three trials using a single-dose protocol showed a smaller effect size that was not statistically significant and there were no admission data in the two trials using a flexible protocol. In absence of significant group difference in this analysis and the absence of head-to-head comparison between treatment protocols, there is insufficient information to judge how these different treatment protocols compare with each other. Until further data are available, it seems reasonable to recommend repeated doses of ipratropium bromide in a fixed protocol for one to two hours.

Asthma exacerbation severity

Examining participant characteristics and study author's classification of severity, it was evident that the overwhelming majority of trials were conducted in children with moderate or severe asthma, or both (not unexpected for studies performed in emergency departments). When the trials were broken down into severity subgroups based on the rate of admission to hospital in the control group (given inhaled SABAs alone) or based on lung function and clinical score, there was no significant difference between the severity subgroups.

The strongest evidence for a 32% and 25% statistically significant reduction in the risk of admission to hospital with an additional inhaled anticholinergic was seen from the trials classified with a high and medium admission rate, respectively, and while no evidence of effect was noted in the subgroup with the lowest admission rates, the small sample in this latter subgroup reduced the precision of this observation. Seven children (95% CI 5 to 12) needed to be treated in the high admission rate subgroup to prevent one hospital admission versus 17 (95% CI 10 to 415) in the medium admission rate subgroup and 139 (not statistically significant) in the low admission rate subgroup (see Table 4). Similarly, although there was no overall statistically significant subgroup difference when severity was based on lung function and clinical score, there was evidence of effect in all severity subgroups but those classified in the mild and mild-moderate severity subgroups. We underline that, irrespective of the severity classification used, as the CIs for these subgroups were overlapping, there was no significant difference in RR or risk difference between the severity subgroups in this group of predominantly moderate and severe children. Until further data are available, it seems prudent to recommend the addition of anticholinergics in children with moderate or severe exacerbations.

Use of systemic corticosteroids

As the use of corticosteroids for the treatment of acute asthma is widely established in practice, we explored the possibility of effect modification by co-intervention with oral corticosteroids (BTS 2011; GINA 2011; Lougheed 2012; Rowe 2001). There was some variation in the use of corticosteroids between studies; corticosteroids were either not used, were systematically used or their use was left to the discretion of the attending physician. We found no statistically significant group difference between the subgroups that did or did not administer systemic corticosteroids and no apparent difference in the size of the effect of an anticholinergic. This suggests that the effect of anticholinergics is not influenced by co-intervention with systemic corticosteroids, at least not within two to three hours of corticosteroid administration (mean time to decision to admit in studies contributing data to the primary outcome two to three hours). This may be due to the delayed onset of action of systemic corticosteroids three to four hours after administration (Rowe 2001).

Other subgroups

Further subgroup analyses were considered for the 2012 update, but not performed. Analysis by age of child was not possible because of the significant overlap in children's ages between studies (see Table 1) and reported data were not stratified by age group in individual studies. Total dose of treatment could not be reliably established as the majority of studies used nebulizer devices to deliver the drug. With such a wide age range of subjects it

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is unclear what proportion of the delivered dose reaches the child's airways (Rubin 2003), which would make any comparison difficult to interpret reliably.

Secondary outcomes

Wide ranges of physiological and spirometric parameters were reported among the studies. However, such was the range of parameters used by different studies that the amount of data that could be pooled were limited.

Statistically significant group differences favoring anticholinergic use were observed for lung function whether reported as 'change in % predicted FEV_1' or as '% change in FEV_1', clinical score at 120 minutes, oxygen saturation at 60 minutes and the need for repeat use of bronchodilators prior to discharge from the emergency department. No significant group difference was seen for the relapse rate.

Adverse events

The combination of anticholinergics and SABAs was associated with a statistically significant 30% and 39% reduced risk of nausea and tremor, respectively. No significant group difference in vomiting was observed. Clinically important adverse effects, such as tachycardia or hypertension, were reported too infrequently to permit aggregation. Thus, the addition of anticholinergics to SABAs decreased the incidence of commonly observed $beta_2$-adrenergic effects in children treated with SABAs only.

Overall completeness and applicability of evidence

The age range of subjects in the included studies ranged from four months to 18 years (with eight studies including preschool-aged children). The diagnosis of asthma in young children represents a considerable challenge to clinicians and wheezy symptoms in children younger than 12 months may represent a different disease process (such as bronchiolitis) to asthma. The inclusion of studies with infants less than 12 months of age was carefully considered for its potential to confound the results. In the studies that included subjects less than 18 months of age (Benito Fernandez 2000; Guill 1987; Phanichyakam 1990), the population age range was examined and in each case less than 5% of the population were under 18 months. With such a degree of homogeneity within the studies, the impact, if any, on the overall review was therefore likely to have been very small. Sensitivity analysis removing the only study (Benito Fernandez 2000) that reported admission data of the three studies that included children less than one year of age, did not alter the direction or magnitude of effect for the primary outcome (RR 0.74; 95% CI 0.63 to 0.86).

With over half of the studies in this review being carried out in North America, the validity of study results to other countries should be considered. Large geographical variations in hospital admission rates have been predominantly attributed to differences in asthma diagnosis, use of daily prophylaxis, intensity of emergency therapy, admission criteria and bed availabilities (Homer 1996; Payne 1995). It is acknowledged in the UK and elsewhere, that admission rates in chronic disease may also be influenced by factors such as population deprivation and availability of primary care services (Saxena 2006). These factors may limit the external validity (generalizability) of study results, but as they would be applied similarly to both the treatment and control group within each study, this would not affect the internal validity of the observed effect. Interestingly, the absence of statistical heterogeneity of study results across trials provides reassurance to the robustness of study results across countries from which these studies originated.

Quality of the evidence

Like all systematic reviews, this meta-analysis is limited by the quality of existing data (Khan 1996). This review examined studies for bias against fixed pre-established criteria in keeping with current Cochrane review methodology. Potential biases were identified in five out of the 19 studies contributing data to our primary outcome. However, there were a far greater number of studies where the potential for bias was unclear. This could be a reflection of poor methodological reporting or poor methodology. Sensitivity analysis removing studies with potential bias did not change the direction and significance of the results for the primary outcome in any of the treatment protocols (Beck 1985; Calvo 1998; Chakraborti 2006; Phanichyakam 1990; Sharma 2004). Data from two unpublished studies (BI [pers comm]; Peterson 1996) were included in this review and sensitivity analysis showed that removing them from the analysis did not impact significantly on the overall result for the primary outcome.

Although only one study clearly described the physician making the decision to admit as blinded to the study medication, the double-blinded nature of nearly all trials (18 out of 20 were double blinded) would imply that study physicians making such clinical decisions were also blinded to the study medication. This should be clearly reported in future trials.

Despite these possible limitations, we did not consider them to have affected the strength or direction of the results for our primary outcome and so we rated the quality of evidence for the effect on hospital admission as high. However, unanswered questions remain regarding the optimal dose, intensity of therapy and severity of asthma exacerbations in relation to the reduced risk of hospital admission.

Potential biases in the review process

We attempted to minimize selection bias in the review process by using a broad search strategy and having the extracted data checked by a member of the editorial base of the Cochrane Airways Group.

Agreements and disagreements with other studies or reviews

The present review summarizes the best evidence available to April 2012. The first update identified three new trials not included in the first version of this review published in 1997. This update has added seven new trials. The conclusion regarding the single-dose protocol and the multiple dose-fixed protocol with regard the primary outcome remains unchanged due to the absence of new trials. With four additional trials in the multiple dose-fixed protocol, the findings of the previous review were confirmed and strengthened. Thus supporting the addition of multiple doses of anticholinergics to SABAs for reducing hospital admission and improving lung function in children not only with severe but also with moderate asthma exacerbations.

The findings of this review are similar to other reviews examining a paediatric population (Rodrigo 2005). In their review, Rodrigo et al included 16 studies examining the use of anticholinergics plus

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SABAs versus SABAs alone in childhood asthma. Of those studies, 15 were examined in this review. Timsit 2002 was excluded from this review as the protocol examined a different dose of SABA in each treatment arm. The review concluded that "the addition of multiple doses of inhaled ipratropium bromide to SABAs is indicated in the standard treatment in children, adolescents and adults with moderate to severe exacerbations of asthma in the emergency setting" (Rodrigo 2005). In line with our definition, Rodrigo 2005 defined severity by baseline spirometric testing (FEV_1 or peak expiratory flow (PEF) 50% to 70% of predicted as moderate exacerbation and FEV_1 or PEF less than 50% of predicted as a severe exacerbation or different clinical scores).

AUTHORS' CONCLUSIONS

Implications for practice

The findings of this Cochrane review support the use of anticholinergics in addition to SABAs over SABAs alone in the management of acute asthma in children, with an anticipated 27% reduction in the risk of hospital admission. The absence of statistically significant subgroup difference in treatment response between severity subgroups or those receiving different treatment intensity (multiple fixed-dose versus single-dose) prevents firm conclusions regarding a possible effect modification associated with treatment intensity and asthma severity. Yet, given the large weight of the trials pertaining to children with moderate or severe asthma (with an under-representation of those with mild asthma) and the absence of effect in the mildest subgroup, it seems prudent to recommend the systematic use of anticholinergics in children with moderate or severe asthma only. Similarly, as most of the evidence is derived from trials testing a multiple fixed-dose protocol using three doses of 250 mcg or two doses of 500 mcg of ipratropium bromide administered by nebulizer over 60 to 90 minutes, in combination with a SABA, we would recommend this treatment strategy and duration. There are also insufficient data to comment on the efficacy of adding anticholinergic to every SABA treatment, that is, titrating the number of both therapies to the child's response, on the optimal duration of combination therapy, and no evidence to explore whether the anticholinergic dose should be adjusted to the child's age. The addition of anticholinergics to SABAs was associated with significantly less tremor and nausea than SABAs alone.

Implications for research

Future trials should be designed to address five issues, the impact on the magnitude of effect of: (1) the severity of airway obstruction (mild asthma and impending respiratory failure); (2) child's age (preschooler-aged versus school-aged children); (3) intensity/flexibility of therapy (fixed versus flexible); (4) dose of anticholinergics (250 mcg versus 500 mcg) and (5) delivery devices (nebulization versus inhalation). This could be done by conducting head-to head comparisons with different doses, treatment intensity (multiple fixed-dose versus multiple flexible-dose protocols) and different inhalation modalities (metered dose inhaler versus nebulization) or by stratifying on child's age and baseline severity or both. Indeed, future research must attempt to define the severity of asthma exacerbation reliably and reproducibly in the study population by standardized methods (e.g. spirometry, respiratory resistance or interrupter technique) or validated clinical scores, or both. Any such attempts should consider the difficulties of using spirometric parameters in a young population (Arets 2001), although it offers the most objective means to ascertain the severity of airway obstruction reliably (Silverman 2007). Alternate measures include use of clinical scores with validated cut-offs for severity such as the Pediatric Respiratory Assessment Measure (Chalut 2000; Ducharme 2008).

Because systemic glucocorticoids are now the standard treatment of children with moderate and severe exacerbations, they should be systematically given with SABAs in future trials. Trials are needed to examine the effect of adding anticholinergics in a multiple flexible-dose manner, that is, each time a SABA is deemed necessary.

Future trials should include more sensitive and reliable endpoints such as number of bronchodilator inhalations and oxygenation (during the emergency department treatment), duration of hospitalisation and duration of need for intensive (at less than four-hour interval) bronchodilator inhalation (for hospitalised children) and attempt to measure time to full recovery in discharged participants, that is, the duration of symptoms, rescue SABA use, functional status and quality of life.

In addition, it seems urgent to assess the efficacy and duration of anticholinergics in children with impending respiratory failure at risk of admission or admitted to the intensive care unit.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Beck 1985

Methods	STUDY DESIGN: parallel LOCATION, NUMBER OF CENTERS: Hospital for sick children, Toronto, Canada DURATION OF STUDY: 7 months
Participants	N SCREENED: not available N RANDOMIZED: 28 N COMPLETED: 25 M = not available F = not available AGE: 6-17.5 years BASELINE DETAILS: FEV_1 < 50% predicted INCLUSION CRITERIA: acute attack, FEV_1 < 50% predicted, able to perform spirometry consistently EXCLUSION CRITERIA: not available
Interventions	PROTOCOL • Fixed: 60 minutes • Observation period: 150 minutes total • Single-dose protocol INTERVENTION GROUP • Salbutamol 150 mcg/kg ((0.03 mL/kg) max 5 mg = 1 mL) then 50 mcg/kg (max 1.7 mg) q20 minutes x 6 • IB 250 mcg at 60 minutes (with fourth salbutamol) CONTROL GROUP • Salbutamol 150 mcg/kg ((0.03 mL/kg) max 5 mg = 1 mL) then 50 mcg/kg (max 1.7 mg) q20 minutes x 6 + placebo CO-INTERVENTION (other medications during study) • Systemic corticosteroids: not described • Theophylline: 6 in each group on regular theophylline; no mention if continued during study FOLLOW-UP PERIOD • Follow-up undertaken but duration not recorded DEVICE • Nebulizer

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Beck 1985 *(Continued)*

Outcomes	PULMONARY FUNCTION TESTS: % change in FEV_1 VITAL SIGNS: pulse, blood pressure, respiratory rate ADVERSE EFFECTS: tremor, vomiting ADMISSION: rate recorded but data not reported RELAPSE: within ? time CRITERIA FOR ADMISSION: not reported
Notes	Author (HL) contacted Confirmation by HL of methodology and data extraction: not obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; other information not available
Allocation concealment (selection bias)	Low risk	Number-coded solutions supplied by pharmacy
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical placebo used
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3 children withdrawn due to protocol errors
Selective reporting (reporting bias)	High risk	Hospital admission data recorded but only reported as "not significantly different"
Other bias	Low risk	

Benito Fernandez 2000

Methods	STUDY DESIGN: parallel LOCATION, NUMBER OF CENTERS: Hospital de Cruces, Vizcaya Spain DURATION OF STUDY: 1 year
Participants	N SCREENED: not reported N RANDOMIZED: 102 N COMPLETED: 102 M = 67 F = 35 AGE: 5 months to 16 years (mean age 5.7 years)

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Benito Fernandez 2000 *(Continued)*

	BASELINE DETAILS: both groups showed similar oxygen saturation and clinical scores at inclusion (oxygen saturations 93.5%, 4.45 and 4.35) (note: clinical score measured 0-5) (described as moderate to severe group) INCLUSION CRITERIA: age 5 months to 16 years, severe acute asthma, previous recurrent wheezing episodes and previous asthma diagnosis EXCLUSION CRITERIA: acute or chronic pulmonary disease other than asthma, and children with their first wheezing episode
Interventions	PROTOCOL • Fixed 60 minutes • Observation period 120 minutes • Multiple fixed-dose protocol INTERVENTION GROUP • IB 250 mcg x 2 with salbutamol (2 doses of 0.2 mg/kg, 6 mg max, 30 minutes apart) CONTROL GROUP • Placebo (normal saline solution) x 2 with salbutamol (2 doses of 0.2 mg/kg, 6 mg max, 30 minutes apart) CO-INTERVENTIONS • Both groups received methylprednisolone 1 mg/kg, 40 mg max (oral administration) FOLLOW-UP PERIOD • 2 weeks DEVICE • Nebulizer
Outcomes	PULMONARY FUNCTION TESTS: PEFR CLINICAL SCORE VITAL SIGNS: oxygen saturation NEED FOR ADDITIONAL SALBUTAMOL NEED TO SEEK MEDICAL ATTENTION IN 2 WEEKS HOSPITALIZATION CRITERIA FOR ADMISSION: not reported
Notes	Translated by Carlos Rodriguez Author not contacted

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation

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Benito Fernandez 2000 *(Continued)*

Allocation concealment (selection bias)	Low risk	The department of pharmacy provided identical packages
Blinding (performance bias and detection bias) All outcomes	Low risk	Both solutions had an identical smell and physical appearance
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for in analysis (no withdrawals)
Selective reporting (reporting bias)	Unclear risk	Unable to ascertain
Other bias	Low risk	

BI [pers comm]

Methods	STUDY DESIGN: parallel LOCATION, NUMBER OF CENTERS: Philippines (multicenter) DURATION OF STUDY: 2002-2003
Participants	N SCREENED: not available N RANDOMIZED: 500 N COMPLETED: 500 M = not available F = not available AGE: 2-10 years BASELINE DETAILS: not available INCLUSION CRITERIA: asthma exacerbation presenting to hospital EXCLUSION CRITERIA: children: with known or suspected hypersensitivity to study drugs, with medical condition that would contraindicate the use of beta$_2$-adrenergic or anticholinergic medications, with first wheezing episode only, with prior intubation for asthma for more than 24 hours, who used ipratropium in 6 hours prior to consultation, with concurrent stridor or possible presence of intrathoracic foreign body, with disease known to have chronic effect on respiratory function (e.g. CF or cardiac disease), requiring immediate resuscitation or airway intervention, with psychiatric disease or psychosocial problems, on other investigational drugs or have used any other investigational drugs within the past month
Interventions	PROTOCOL: • Fixed: 60 minutes • Observation period: 100 minutes • Multiple fixed-dose protocol INTERVENTION GROUP • Combivent UDV (ipratropium 500 mcg and salbutamol 2.5 mg), 1 UDV every 20 minutes for 3 doses

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BI [pers comm] *(Continued)*

	CONTROL GROUP • Salbutamol 2.5 mg UDV, 1 UDV every 20 minutes for 3 doses DEVICE • Inhalation
Outcomes	ASTHMA SEVERITY SCORE NUMBER OF CHILDREN ASSESSED TO BE NEEDING HOSPITALIZATION AMOUNT OF ADDITIONAL RESCUE MEDICATION O_2 SATURATION NUMBER OF DISCHARGED CHILDREN REVISITING THE EMERGENCY DEPARTMENT OR DOCTOR'S CLINIC WITHIN 24 HOURS CRITERIA FOR ADMISSION: not reported
Notes	Unpublished trial data supplied by Boehringer Ingelheim (Phil.) Inc

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; other information not available
Allocation concealment (selection bias)	Unclear risk	Information not available; other information not available
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double blind; other information not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 withdrawals due to adverse events (1 in each group)
Selective reporting (reporting bias)	Unclear risk	Cannot ascertain this
Other bias	Unclear risk	Cannot ascertain this

Calvo 1998

Methods	STUDY DESIGN: parallel LOCATION, NUMBER OF CENTERS: Valdivia City, Chile DURATION OF STUDY: fall and winter
Participants	N SCREENED: not available N RANDOMIZED: 40 N COMPLETED: 40

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Calvo 1998 *(Continued)*

	M = 47 F = 33 AGE: 5-14 years BASELINE DETAILS: PEF < 80% predicted and Tal Score > 5 INCLUSION CRITERIA: perform spirometry EXCLUSION CRITERIA: cardiac failure, lung disease, needed to be hospitalised, experienced a first acute bronchial obstruction, had hypersensitivity to the medications used, were treated 8 hours before the onset of this study
Interventions	PROTOCOL • Titrated to child until symptoms controlled • Observation period: 120 minutes • Multiple flexible-dose protocol INTERVENTION GROUP • Salbutamol 200 mcg + IB 40 mcg q15 minutes x 4 then q20 minutes x 3 CONTROL GROUP • Salbutamol 200 mcg q15 minutes x 4 then q20 minutes x 3 CO-INTERVENTION (other medications used during study) • Some children received systemic corticosteroids (prednisone 1 mg/kg/dose: max = 40 mg) at 60 minutes after beginning treatment if "no clinical or laboratory improvement" FOLLOW-UP • 120 minutes DEVICE • Inhalation
Outcomes	PULMONARY FUNCTION TESTS: peak flow CLINICAL SCORE: Tal score VITAL SIGNS: pulse, respiratory rate ADVERSE EFFECTS: tremor, mydriatic reaction, dryness of the oral membrane, pharyngeal irritation, nausea, vomiting NUMBER OF CHILDREN NEEDING CORTICOSTEROIDS ADMISSION CRITERIA FOR ADMISSION: not reported
Notes	Author (GMC) contacted Confirmation by GMC of methodology and data extraction obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Consecutive assignment

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Calvo 1998 *(Continued)*

Allocation concealment (selection bias)	Low risk	Number-coded solutions supplied by pharmacy
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed
Selective reporting (reporting bias)	Low risk	None noted
Other bias	Low risk	None identified

Chakraborti 2006

Methods	STUDY DESIGN: parallel LOCATION, NUMBER OF CENTERS: paediatric chest clinic in Tertiary Hospital, North India DURATION OF STUDY: 1 year 6 months
Participants	N SCREENED: not available N RANDOMIZED: 60 N COMPLETED: 60 M = 36 F = 24 AGE: 5-15 years BASELINE DETAILS: mild to moderate acute exacerbation of asthma (FEV_1 < 80% predicted) INCLUSION CRITERIA: able to perform spirometry EXCLUSION CRITERIA: severe acute exacerbation, co-existing cardiac or renal disease, intolerance to study medication, glaucoma, urinary retention, use of oral bronchodilator in last 12 hours
Interventions	PROTOCOL • Fixed 0 minutes • Observation period: 30 minutes • Single-dose protocol INTERVENTION GROUP • 4 x salbutamol 100 mcg via MDI and spacer + 4 x IB 20 mcg CONTROL • 4 x salbutamol 100 mcg via MDI and spacer + 4 x placebo TREATMENT PERIOD CO-INTERVENTIONS

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Chakraborti 2006 *(Continued)*

	• None FOLLOW-UP PERIOD • 30 minutes DEVICE • MDI
Outcomes	HOSPITALIZATION PULMONARY FUNCTION TESTS: FEV^1 , FEV_1%, FVC, FVC%, FEF^{25-75} , FEF%, FEV_1/FVC, PEFR, PEFR% VITAL SIGNS: heart rate CLINICAL SCORE: wheeze score, accessory muscle score, clinical asthma score CRITERIA FOR ADMISSION: not reported
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated blocks of 6
Allocation concealment (selection bias)	Low risk	"A person not involved in the study evaluation did the labelling"
Blinding (performance bias and detection bias) All outcomes	Low risk	"...similar looking MDIs..." "...10 resident doctors were asked to identify labelled MDIs as to which contained drug and placebo. Only 1 resident could identify the MDIs (placebo or ipratropium) correctly. 90% cases failed to identify"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data available for 60 children randomised
Selective reporting (reporting bias)	Low risk	All data relevant to outcomes in this review were reported in full
Other bias	High risk	Data only available for 30 minutes post-treatment

Cook 1985

Methods	STUDY DESIGN: parallel LOCATION, NUMBER OF CENTERS: Christchurch Hospital, Christchurch, New Zealand DURATION OF STUDY: not available
Participants	N SCREENED: not available N RANDOMIZED: 48

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Cook 1985 *(Continued)*

	N COMPLETED: 45 M = 26 F = 22 AGE: 18 months to 12 years BASELINE DETAILS: "moderately severe" INCLUSION CRITERIA: moderately severe asthma exacerbation EXCLUSION CRITERIA: children deemed to require intravenous therapy
Interventions	PROTOCOL • Fixed • Observation period: 120 minutes • Single-dose protocol (with additional doses determined by clinical need) INTERVENTION GROUP • Fenoterol 0.125 mL (1-4 y.o.)/0.25 mL (5-8 y.o.)/0.5 mL (9-12 y.o.) + IB 1 mL (1-4 y.o.)/1.5 mL (5-8 y.o.)/2.0 mL (9-12 y.o.) CONTROL GROUP • Fenoterol 0.125 mL (1-4 y.o.)/0.25 mL (5-8 y.o.)/0.5 mL (9-12 y.o.) + placebo CO-INTERVENTION (other medications used during study) • None FOLLOW-UP: • None DEVICE • Nebulizer
Outcomes	CHANGE IN CLINICAL SCORE: overall score of wheeze, air entry and respiratory distress VITAL SIGNS: pulse, respiratory rate NEED FOR REPEAT TREATMENTS AFTER STANDARD PROTOCOL PRIOR TO DISPOSITION
Notes	Co-author (KPD) contacted Confirmation by KPD of methodology: obtained Confirmation of data extraction: pending For change in clinical score, no values for t = 0 minutes, therefore used t = 5 minutes as baseline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; other information not available
Allocation concealment (selection bias)	Unclear risk	Information not available

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Cook 1985 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Identical placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Three patients (1 in each group) required intravenous therapy and did not complete the trial. The results from these patients were excluded from the analysis"
Selective reporting (reporting bias)	Low risk	None identified
Other bias	Low risk	None identified

Ducharme 1998

Methods	STUDY DESIGN: parallel LOCATION, NUMBER OF CENTERS: Montreal Children's Hospital, Canada DURATION OF STUDY: 30 months
Participants	N SCREENED: 858 N RANDOMIZED: 298 N COMPLETED: 298 M = 182 F = 116 AGE: 3-17 years BASELINE DETAILS: "mild to moderate" asthma attack INCLUSION CRITERIA: exacerbation of mild or moderate severity requiring more than 1 nebulization of salbutamol. Ability to perform respiratory resistance consistently EXCLUSION CRITERIA: children with severe asthma, in whom short delay for documenting baseline respiratory resistance appeared unacceptable or in whom continuous nebulizations of salbutamol were prescribed
Interventions	PROTOCOL • Fixed: 60 minutes • Observation period: 210 minutes • Single-dose protocol INTERVENTION GROUP - combination of: • Salbutamol 0.15 mg/kg q1 hour + IB 250 mcg (single dose) OR • Salbutamol 0.075 mg/kg q30 minutes + IB 250 mcg CONTROL GROUP - combination of: • Salbutamol 0.15 mg/kg q1 hour + placebo OR • Salbutamol 0.075 mg/kg q30 minutes + placebo CO-INTERVENTION (other medications used during study)

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Ducharme 1998 *(Continued)*

	• Systemic corticosteroids: at discretion of treating physician FOLLOW-UP • 10 days DEVICE • Nebulizer
Outcomes	PULMONARY FUNCTION TESTS: % change in RFo CHANGE IN CLINICAL SCORE: Wheezing score O_2 SATURATION # REPEAT TREATMENTS REQUIRED AFTER STANDARD PROTOCOL PRIOR TO DISPOSITION VITAL SIGNS: pulse ADVERSE EFFECTS: tremor, vomiting, nausea NEED FOR CORTICOSTEROIDS PRIOR TO DISCHARGE ADMISSION RELAPSE: within 72 hours RELAPSE ADVERSE EFFECTS: not described CRITERIA FOR ADMISSION: not reported
Notes	Author (FMD) contacted Confirmation by FMD of methodology and data extraction obtained Factorial design - tested 2 interventions simultaneously (frequent low doses of salbutamol + combination therapy with IB); no interaction observed between the 2 interventions

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Coded solutions
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	No evidence of unreported outcomes
Other bias	Low risk	No other bias identified

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Guill 1987

Methods	STUDY DESIGN: parallel LOCATION, NUMBER OF CENTERS: Medical College of Georgia, USA DURATION OF STUDY: not available
Participants	N SCREENED: not available N RANDOMIZED: 44 N COMPLETED: 44 M = 26 F = 18 AGE: 13 months to 13 years BASELINE DETAILS: not available INCLUSION CRITERIA: bronchospasm for which bronchodilator treatment was considered necessary EXCLUSION CRITERIA: not available
Interventions	PROTOCOL • Titrated to child until symptoms controlled or child admitted TEST GROUP • Metaproterenol 0.2 mL (< 12 y.o.)/0.3 mL (≥ 12 y.o.) + atropine sulfate 0.05-0.1 mg/kg (max 2 mg) CONTROL GROUP • Metaproterenol 0.2 mL (< 12 y.o.)/0.3 mL (≥ 12 y.o.) CO-INTERVENTION (other medications used during study) • Systemic corticosteroids: not mentioned FOLLOW-UP • 48 hours DEVICE • Nebulizer
Outcomes	PULMONARY FUNCTION TESTS: change in % predicted PEF CLINICAL SCORE: pulmonary index NUMBER OF REPEAT TREATMENTS REQUIRED PRIOR TO DISPOSITION ADVERSE EFFECTS: no details in study given but data confirmed ADMISSION: data not available RELAPSE: data not available
Notes	Author (MFG) contacted Confirmation by MFG of methodology and data extraction obtained
Risk of bias	

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Guill 1987 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Opaque consecutive numbered envelopes containing assignment
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical placebos used
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the trial and were included in the analysis
Selective reporting (reporting bias)	Low risk	No evidence of unreported outcomes
Other bias	Low risk	No other bias identified

Iramain 2011

Methods	STUDY DESIGN: parallel randomised double-blind trial LOCATION, NUMBER OF CENTERS: emergency department, location not reported DURATION OF STUDY: not available
Participants	N SCREENED: not available N RANDOMIZED: 106 N COMPLETED: 97 (49 salbutamol + ipratropium; 48 salbutamol + placebo) M = 49% F = 51% AGE: 2-18 years BASELINE DETAILS: moderate to severe asthma INCLUSION CRITERIA: children presenting with moderate to severe asthma crises (episode of respiratory difficulty and wheezing associated with the use of intercostal muscles or subcostal retraction and fall in PEF and FEV_1). EXCLUSION CRITERIA: mild asthma crisis, administration of corticosteroids in the previous 24 hours, presence of severe respiratory failure requiring admission to ICU or mechanical ventilation, history of respiratory failure requiring admission to ICU, cardiac or pulmonary malfunction, chronic lung disease (pulmonary bronchodysplasia, CF), stridor, foreign body aspiration, neurologic alterations or contraindications for the use of SABAs or anticholinergic medications
Interventions	PROTOCOL: • Multiple fixed-dose: 6 nebulizations of salbutamol + placebo or 6 nebulizations if salbutamol + IB • Observation period: 30, 60, 90, 120 and 240 minutes at which point it was decide whether to admit INTERVENTION GROUP

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Iramain 2011 *(Continued)*

- Salbutamol 5 mg + IB (40 drops 500 mcg) in 5 mL saline. 2.5 mL solution given to children weighing less than 20 kg and 5 mL in heavier children

CONTROL GROUP

- Salbutamol 5 mg in 5 mL saline. 2.5 mL solution given to children weighing less than 20 kg and 5 mL in heavier children

RUN-IN PERIOD

- None

CO-INTERVENTIONS

- None

FOLLOW-UP

- 30, 60, 90, 120 and 240 minutes

CRITERIA FOR ADMISSION

- Asthma score < 7 and oxygen saturation < 94% or PEF or FEV_1 < 60% predicted

DEVICE

- Jet-type nebulizer

Outcomes	FEV_1 at 30, 60, 90, 120 and 240 minutes Hospital admission
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"After obtaining informed consent from parents, patients were randomised using a computer generated sequence"
Allocation concealment (selection bias)	Low risk	Numbered bottles protect allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	"The hospital pharmacy department prepared two types of numbered plastic bottles.... The two solutions have the same smell, colour and fluid level in order to prevent differentiation. Neither the investigators nor the patients knew which solution the bottles contained"
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 dropouts (2 from salbutamol + ipratropium due to tachycardia and 1 ICU admission; 1 from salbutamol due to tachycardia)
Selective reporting (reporting bias)	Unclear risk	No trial protocol found
Other bias	Unclear risk	None identified

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Peterson 1996

Methods	RANDOMIZATION METHOD: computer generated random numbers MEANS: number-coded solutions supplied by the pharmacy BLINDING: triple-blinding, identical placebo WITHDRAWAL/DROPOUT: described LOCATION: Canada
Participants	N = 163 (IB + salbutamol N = 82, salbutamol only N = 81) AGE: 5-12 years BASELINE SEVERITY: < 70% predicted FEV_1 OTHER: ability to perform spirometry consistently
Interventions	PROTOCOL • Fixed: 90 minutes • Observation period: 120 minutes total • Multiple flexible-dose protocol INTERVENTION GROUP • Salbutamol 3 mg + IB 250 mcg q45 minutes x 2 doses CONTROL GROUP • Salbutamol 3 mg q45 minutes x 2 doses CO-INTERVENTION (other medications used during study) • Additional inhalation of salbutamol + placebo/ipratropium at 90 minutes if FEV_1 < 85% of predicted • Systemic corticosteroids: at discretion of treating physician • Other medications: documented DEVICE • Nebulizer
Outcomes	PULMONARY FUNCTION TESTS: change in % predicted FEV_1, change in predicted PEF O_2 SATURATION # REPEAT TREATMENTS REQUIRED AFTER STANDARD PROTOCOL PRIOR TO DISPOSITION VITAL SIGNS: blood pressure, pulse, respiratory rate ADVERSE EFFECTS: rash, dizziness, hyperkinesia, hypertonia, tremor, conjunctivitis, taste perversion, vomiting, abdominal pain, nausea, coughing, epistaxis, pneumonia, pneumothorax, asthma exacerbation, headache, chest pain, fever, pain, sinusitis, stridor, bacterial infection NEED FOR CORTICOSTEROIDS PRIOR TO DISPOSITION ADMISSION CRITERIA FOR ADMISSION: not reported RELAPSE: within 72 hours
Notes	Unpublished multicenter trial Co-investigator (TK) contacted and granted permission to use unpublished data Confirmation by TK of methodology and data extraction obtained

Risk of bias

Bias	Authors' judgement	Support for judgement

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Peterson 1996 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Number-coded solutions supplied by the pharmacy
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical placebo
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Cannot be ascertained
Selective reporting (reporting bias)	Unclear risk	Cannot be ascertained
Other bias	Unclear risk	Insufficient details provided (unpublished data)

Phanichyakam 1990

Methods	STUDY DESIGN: parallel LOCATION, NUMBER OF CENTERS: Ramathibodi Hospital, Bangkok, Thailand DURATION OF STUDY: not available
Participants	N SCREENED: not available N RANDOMIZED: 20 N COMPLETED: 20 M = 14 F = 6 AGE: 4 months to 15 years BASELINE DETAILS: not available INCLUSION CRITERIA: not available EXCLUSION CRITERIA: not available
Interventions	PROTOCOL • Fixed: 15 minutes • Observation period: 360 minutes total • Single dose INTERVENTION GROUP • Terbutaline 0.5 mg + IB 0.04 mg (15 minutes after terbutaline) x 1 dose CONTROL GROUP • Terbutaline 0.5 mg x 1 dose CO-INTERVENTION (other medications used during study)

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Phanichyakam 1990 *(Continued)*

	• Not mentioned FOLLOW-UP • 360 minutes DEVICE • MDI with 750 cc volumetric spacer
Outcomes	PULMONARY FUNCTION TESTS: % change in FEV_1, % change in PEF VITAL SIGNS: blood pressure, heart rate, respiratory rate ADVERSE EFFECTS: 'ocular', 'secretion-drying', 'facial-flushing'
Notes	Contact of 3 authors attempted but unsuccessful Confirmation of methodology and data extraction not obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; no other information available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	High risk	"Each child received either 0.5 mg (2 puffs) of inhaled terbutaline or inhaled terbutaline 0.5 mg + inhaled IB 0.04mg (2 puffs) 15 minutes later"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study
Selective reporting (reporting bias)	Low risk	No unreported outcomes identified
Other bias	Low risk	No other bias identified

Qureshi 1997

Methods	STUDY DESIGN: parallel LOCATION, NUMBER OF CENTERS: Hospital of The King's Daughters, Virginia, USA DURATION OF STUDY: 11 months
Participants	N SCREENED: not available N RANDOMIZED: 90 N COMPLETED: 90 M = 55 F = 35

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Qureshi 1997 *(Continued)*

	AGE: 6-18 years BASELINE DETAILS: < 50% predicted PEFR INCLUSION CRITERIA: asthma exacerbation: difficulty breathing, wheezing and worsening of the child's usual symptoms or deterioration of pulmonary functions. The ability to perform reliable pulmonary function testing EXCLUSION CRITERIA: evidence of an intrathoracic foreign body, high clinical suspicion of pneumonia, concurrent stridor, any disease process known to chronically affect respiratory function
Interventions	PROTOCOL • Fixed: 60 minutes • Observation period: 120 minutes total • Multiple doses INTERVENTION GROUP • Albuterol 0.15 mg/kg/dose q30 minutes + ipratropium 500 mcg at 0 and 60 minutes CONTROL GROUP • Albuterol 0.15 mg/kg/dose q30 minutes + saline at 0 and 60 minutes CO-INTERVENTION (other medications used during the study) • Systemic corticosteroids: all received oral corticosteroids at 60 minutes FOLLOW-UP • 48 hours DEVICE • Nebulizer
Outcomes	PULMONARY FUNCTION TESTS: Change in predicted FEV_1, Change in predicted PEF O_2 SATURATION VITAL SIGNS: blood pressure, heart rate, respiratory rate ADVERSE EFFECTS: increasing breathlessness, dry mouth, palpitations, blurred vision, dilation of pupils, nausea, vomiting, mental confusion, dizziness, headache, back and chest pain # REPEAT TREATMENTS REQUIRED AFTER STANDARD PROTOCOL PRIOR TO DISPOSITION ADMISSION CRITERIA FOR ADMISSION: oxygen saturations < 94% RELAPSE: within 48 hours
Notes	Author (FQ) contacted Confirmation by FQ of methodology and data extraction obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers

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Qureshi 1997 *(Continued)*

Allocation concealment (selection bias)	Low risk	Number-coded solutions supplied by the pharmacy
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	No unreported outcomes identified
Other bias	Low risk	No other sources of bias identified

Qureshi 1998

Methods	STUDY DESIGN: parallel LOCATION, NUMBER OF CENTERS: Hospital of The King's Daughters, Virginia, USA DURATION OF STUDY: 8 months
Participants	N SCREENED: not available N RANDOMIZED: 480 N COMPLETED: 434 M = 248 F = 186 AGE: 2-18 years (163 moderate group) BASELINE DETAILS: < 70% predicted PEFR INCLUSION CRITERIA: asthma exacerbation: increased difficulty breathing, wheezing and worsening of the child's usual symptoms or deterioration of PEFR EXCLUSION CRITERIA: treatment with ipratropium within 6 hours before the visit, a disease known to have a chronic effect on respiratory function, concurrent stridor, possible presence of an intrathoracic foreign body, a medical condition that would contraindicate the use of $beta_2$ adrenergic or anticholinergic medications, or need for immediate resuscitation or airway intervention
Interventions	PROTOCOL • Fixed: 60 minutes • Observation period: up to 248 minutes • Multiple doses INTERVENTION GROUP • Albuterol 2.5 mg (< 20 kg)/5.0 mg (≥ 20 kg) q20 minutes x 3 + IB 500 mcg at 20 and 40 minutes CONTROL GROUP

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Qureshi 1998 *(Continued)*

- Albuterol 2.5 mg (< 20 kg)/5.0 mg (≥ 20 kg) q20 minutes x 3 + saline at 20 and 40 minutes

CO-INTERVENTION (other medications used during the study)

- Systemic corticosteroids - all received oral corticosteroids at 20 minutes

FOLLOW-UP

- 72 hours

DEVICE

- Nebulizer

Outcomes	PULMONARY FUNCTION TESTS: % change in PEFR CHANGE IN CLINICAL SCORE O_2 SATURATION # NEBULIZER TREATMENTS UNTIL DISPOSITION TIME TO DISPOSITION VITAL SIGNS: pulse, respiratory rate ADMISSION CRITERIA FOR ADMISSION: "objective changes in clinical and pulmonary function and oxygen saturations in air" (saturations > 94% in air were accepted) RELAPSE
Notes	Author (FQ) contacted Confirmation by FQ of methodology and data extraction obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Low risk	Number-coded solutions supplied by pharmacy
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical placebo
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	In 46 children, symptoms resolved before the second dose of the study medication. 18 received a single dose of albuterol and improved. Of the remaining 26 children who had a moderate exacerbation, the split between treatment groups was even (14 and 12). This does not affect the results for outcome: hospital admission, but it may introduce bias in clinical scores since data would be collected on those children more likely to experience a change in their scores over the course of the trial protocol
Selective reporting (reporting bias)	Low risk	None identified
Other bias	Low risk	None identified

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Qureshi 1998 (moderate)

Methods	STUDY DESIGN: parallel LOCATION, NUMBER OF CENTERS: Hospital of The King's Daughters, Virginia, USA DURATION OF STUDY: 8 months
Participants	N SCREENED: not available N RANDOMIZED: 480 N COMPLETED: 434 M = 248 F = 186 AGE: 2-18 years (163 moderate group) BASELINE DETAILS: < 70% predicted PEFR INCLUSION CRITERIA: asthma exacerbation: increased difficulty breathing, wheezing and worsening of the child's usual symptoms or deterioration of PEFR EXCLUSION CRITERIA: treatment with ipratropium within 6 hours before the visit, a disease known to have a chronic effect on respiratory function, concurrent stridor, possible presence of an intrathoracic foreign body, a medical condition that would contraindicate the use of beta$_2$ adrenergic or anticholinergic medications, or need for immediate resuscitation or airway intervention
Interventions	PROTOCOL • Fixed: 60 minutes • Observation period: up to 248 minutes • Multiple doses INTERVENTION GROUP • Albuterol 2.5 mg (< 20 kg)/5.0 mg (≥ 20 kg) q20 minutes x 3 + IB 500 mcg at 20 and 40 minutes CONTROL GROUP • Albuterol 2.5 mg (< 20 kg)/5.0 mg (≥ 20 kg) q20 minutes x 3 + saline at 20 and 40 minutes CO-INTERVENTION (other medications used during the study) • Systemic corticosteroids - all received oral corticosteroids at 20 minutes FOLLOW-UP • 72 hours DEVICE • Nebulizer
Outcomes	PULMONARY FUNCTION TESTS: % change in PEFR CHANGE IN CLINICAL SCORE O_2 SATURATION # NEBULIZER TREATMENTS UNTIL DISPOSITION TIME TO DISPOSITION VITAL SIGNS: pulse, respiratory rate

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Qureshi 1998 (moderate) *(Continued)*

	ADMISSION CRITERIA FOR ADMISSION: "objective changes in clinical and pulmonary function and oxygen saturations in air" (saturations > 94% in air were accepted) RELAPSE
Notes	Author (FQ) contacted Confirmation by FQ of methodology and data extraction obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Low risk	Number-coded solutions supplied by pharmacy
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	In 46 children symptoms resolved before the second dose of the study medication. 18 received a single dose of albuterol and improved. Of the remaining 26 children who had a moderate exacerbation, the split between treatment groups was even (14 and 12). This does not affect the results for outcome: hospital admission, but it may introduce bias in clinical scores since data would be collected on those children more likely to experience a change in their scores over the course of the trial protocol
Selective reporting (reporting bias)	Low risk	None identified
Other bias	Low risk	None identified

Qureshi 1998 (severe)

Methods	STUDY DESIGN: parallel LOCATION, NUMBER OF CENTERS: Hospital of The King's Daughters, Virginia, USA DURATION OF STUDY: 8 months
Participants	N SCREENED: not available N RANDOMIZED: 480 N COMPLETED: 434 M = 248 F = 186 AGE: 2-18 years (271 severe group)

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Qureshi 1998 (severe) *(Continued)*

	BASELINE DETAILS: < 50% predicted PEFR INCLUSION CRITERIA: asthma exacerbation: increased difficulty breathing, wheezing and worsening of the child's usual symptoms or deterioration of PEFR EXCLUSION CRITERIA: treatment with ipratropium within 6 hours before the visit, a disease known to have a chronic effect on respiratory function, concurrent stridor, possible presence of an intrathoracic foreign body, a medical condition that would contraindicate the use of beta$_2$ adrenergic or anticholinergic medications, or need for immediate resuscitation or airway intervention
Interventions	PROTOCOL • Fixed: 60 minutes • Observation period: up to 248 minutes • Multiple doses INTERVENTION GROUP • Albuterol 2.5 mg (< 20 kg)/5.0 mg (≥ 20 kg) q20 minutes x 3 + IB 500 mcg at 20 and 40 minutes CONTROL GROUP • Albuterol 2.5 mg (< 20 kg)/5.0 mg (≥ 20 kg) q20 minutes x 3 + saline at 20 and 40 minutes CO-INTERVENTION (other medications used during the study) • Systemic corticosteroids - all received oral corticosteroids at 20 minutes FOLLOW-UP • 72 hours DEVICE • Nebulizer
Outcomes	PULMONARY FUNCTION TESTS: % change in PEFR CHANGE IN CLINICAL SCORE O_2 SATURATION # NEBULIZER TREATMENTS UNTIL DISPOSITION TIME TO DISPOSITION VITAL SIGNS: pulse, respiratory rate ADMISSION CRITERIA FOR ADMISSION: "objective changes in clinical and pulmonary function and oxygen saturations in air" (saturations > 94% in air were accepted) RELAPSE
Notes	Author (FQ) contacted Confirmation by FQ of methodology and data extraction obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers

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Qureshi 1998 (severe) *(Continued)*

Allocation concealment (selection bias)	Low risk	Number-coded solutions supplied by pharmacy
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	In 46 children symptoms resolved before the second dose of the study medication. 18 received a single dose of albuterol and improved. Of the remaining 26 children who had a moderate exacerbation, the split between treatment groups was even (14 and 12). This does not affect the results for outcome: hospital admission, but it may introduce bias in clinical scores since data would be collected on those children more likely to experience a change in their scores over the course of the trial protocol
Selective reporting (reporting bias)	Low risk	None identified
Other bias	Low risk	None identified

Reisman 1988

Methods	STUDY DESIGN: parallel LOCATION, NUMBER OF CENTERS: Hospital for Sick Children, Toronto, Canada DURATION OF STUDY: 12 months
Participants	N SCREENED: not available N RANDOMIZED: 25 N COMPLETED: 24 M = not available F = not available AGE: 5-15 years BASELINE DETAILS: < 55% predicted FEV_1 INCLUSION CRITERIA: children who could perform spirometry and < 55% predicted FEV_1 EXCLUSION CRITERIA: not available
Interventions	PROTOCOL • Fixed: 80 minutes • Observation period: 150 minutes total • Multiple doses INTERVENTION GROUP • Salbutamol 150 mcg/kg ((0.03 mL/kg) max 5 mg = 1 mL)) then 50 mcg/kg q20 minutes x 6 + IB 250 mcg at 0, 40 and 80 minutes CONTROL GROUP

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Reisman 1988 *(Continued)*

- Salbutamol 150 mcg/kg ((0.03 mL/kg) max 5 mg = 1 mL)) then 50 mcg/kg q20 minutes x 6

CO-INTERVENTION (other medications used during study)

- Systemic corticosteroids: none
- Theophylline: none

FOLLOW-UP

- 150 minutes

DEVICE

- Nebulizer

Outcomes	PULMONARY FUNCTION TESTS: change in % predicted FEV_1 CHANGE IN WHEEZING SCORE ADMISSION CRITERIA FOR ADMISSION: not reported RELAPSE: not reported ADVERSE EFFECTS: tremor, vomiting
Notes	Author (HL) contacted Confirmation of methodology and data extraction not obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; no other information available
Allocation concealment (selection bias)	Low risk	Number-coded solutions supplied by the pharmacy
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 subject not completing the study was too tired to co-operate with the spirometry
Selective reporting (reporting bias)	Low risk	None identified
Other bias	Low risk	None identified

Schuh 1995

Methods	STUDY DESIGN (parallel, cross-over): Parallel LOCATION, NUMBER OF CENTERS: Hospital for Sick Children, Toronto, Canada DURATION OF STUDY: 2 years 2 months
Participants	N SCREENED: 1586

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Schuh 1995 *(Continued)*

	N RANDOMIZED: 79 N COMPLETED: unclear M = not available F = not available AGE: 5-17 years BASELINE DETAILS: FEV_1 < 50% predicted INCLUSION CRITERIA: acute asthma attack, were able to perform the pulmonary function testing reliably, FEV_1 < 50% predicted EXCLUSION CRITERIA: children with 1st wheezing episode, used IB in last 4 hours prior to study start, previous PICU admission, concurrent cardiopulmonary disease, near death and requiring immediate intervention, known hypersensitivity to study drugs.
Interventions	PROTOCOL • Fixed: 60 minutes • Observation period: 120 minutes total • Single and multiple doses TEST GROUPS • Albuterol 0.15 mg/kg q20 minutes x 3 + IB 250 mcg x 1 OR • Albuterol 0.15 mg/kg q20 minutes x 3 + IB 250 mcg q20 minutes x 3 CONTROL GROUP • Albuterol 0.15 mg/kg q20 minutes x 3 RUN-IN PERIOD: none CO-INTERVENTION (other medications used during study) • Systemic corticosteroids: none • Other medications: no bronchodilators FOLLOW-UP • 72 hours DEVICE • Nebulizer
Outcomes	PULMONARY FUNCTION TESTS - change in % predicted FEV_1 OXYGEN SATURATION CHANGE IN CLINICAL SCORE: accessory muscle, wheeze, dyspnoea and overall # REPEAT TREATMENTS REQUIRED AFTER STANDARD PROTOCOL PRIOR TO DISPOSITION VITAL SIGNS: heart rate, respiratory rate ADVERSE EFFECTS: nausea, tremor, conjunctivitis, coughing spasm with syncope ADMISSION: described 'children with respiratory distress' RELAPSE: within 72 hours
Notes	Author (SS) contacted Confirmation of methodology and data extraction obtained

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Schuh 1995 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Low risk	Number-coded solutions supplied by the pharmacy
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 parent changed his mind and demanded withdrawal before the start of experimental therapy. "Seven patients had to stop the trial prematurely at either 60 or 80 minutes; three children (one each in groups 1, 2 and 3) stopped cooperating before the 120 minute measurement, and three children in group 2 and one child in group 3 were too ill to continue. Two patients had missing data at 80 minutes (because of vomiting) but both had recovered by 120 minutes"
Selective reporting (reporting bias)	Low risk	None identified
Other bias	Low risk	None identified

Schuh 1995 (multiple)

Methods	See table Schuh 1995
Participants	N SCREENED: 1586 N RANDOMIZED: 81 N COMPLETED: unclear M = not available F = not available AGE: 5-17 years BASELINE DETAILS: FEV_1 < 50% predicted
Interventions	PROTOCOL • Fixed: 60 minutes • Observation period: 120 minutes total • Multiple doses TEST GROUPS • Albuterol 0.15 mg/kg q20 minutes x 3 + IB 250 mcg q20 minutes x 3 CONTROL GROUP • Albuterol 0.15 mg/kg q20 minutes x 3 RUN-IN PERIOD

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Schuh 1995 (multiple) *(Continued)*

	• None CO-INTERVENTION (other medications used during study) • Systemic corticosteroids: none • Other medications: no bronchodilators FOLLOW-UP • 72 hours DEVICE • Nebulizer
Outcomes	PULMONARY FUNCTION TESTS - change in % predicted FEV_1 OXYGEN SATURATION CHANGE IN CLINICAL SCORE: accessory muscle, wheeze, dyspnoea and overall # REPEAT TREATMENTS REQUIRED AFTER STANDARD PROTOCOL PRIOR TO DISPOSITION VITAL SIGNS: heart rate, respiratory rate ADVERSE EFFECTS: nausea, tremor, conjunctivitis, coughing spasm with syncope ADMISSION: described 'children with respiratory distress' RELAPSE: within 72 hours
Notes	Author (SS) contacted Confirmation of methodology and data extraction obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Low risk	Number-coded solutions supplied by the pharmacy
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 parent changed his mind and demanded withdrawal before the start of experimental therapy. "Seven patients had to stop the trial prematurely at either 60 or 80 minutes; three children (one each in groups 1, 2 and 3) stopped cooperating before the 120 minute measurement, and three children in group 2 and one child in group 3 were too ill to continue. Two patients had missing data at 80 minutes (because of vomiting) but both had recovered by 120 minutes"
Selective reporting (reporting bias)	Low risk	None identified
Other bias	Low risk	None identified

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Schuh 1995 (single)

Methods	See table Schuh 1995
Participants	N SCREENED: 1586 N RANDOMIZED: 79 N COMPLETED: unclear M = not available F = not available AGE: 5-17 years BASELINE DETAILS: FEV_1 < 50% predicted INCLUSION CRITERIA: acute asthma attack, were able to perform the pulmonary function testing reliably, FEV_1 < 50% predicted EXCLUSION CRITERIA: children with first wheezing episode, used IB in last 4 hours prior to study start, previous PICU admission, concurrent cardiopulmonary disease, near death and requiring immediate intervention, known hypersensitivity to study drugs
Interventions	PROTOCOL • Fixed: 60 minutes • Observation period: 120 minutes total • Single dose TEST GROUPS • Albuterol 0.15 mg/kg q20 minutes x 3 + IB 250 mcg x 1 CONTROL GROUP • Albuterol 0.15 mg/kg q20 minutes x 3 RUN-IN PERIOD • None CO-INTERVENTION (other medications used during study) • Systemic corticosteroids: none • Other medications: no bronchodilators FOLLOW-UP • 72 hours DEVICE • Nebulizer
Outcomes	PULMONARY FUNCTION TESTS - Change in % predicted FEV_1 OXYGEN SATURATION CHANGE IN CLINICAL SCORE: accessory muscle, wheeze, dyspnoea and overall # REPEAT TREATMENTS REQUIRED AFTER STANDARD PROTOCOL PRIOR TO DISPOSITION VITAL SIGNS: heart rate, respiratory rate ADVERSE EFFECTS: nausea, tremor, conjunctivitis, coughing spasm with syncope ADMISSION: described 'children with respiratory distress' RELAPSE: within 72 hours

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Schuh 1995 (single) *(Continued)*

Notes	Author (SS) contacted Confirmation of methodology and data extraction obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Number-coded solutions supplied by the pharmacy
Allocation concealment (selection bias)	Low risk	Identical placebo
Blinding (performance bias and detection bias) All outcomes	Low risk	1 parent changed his mind and demanded withdrawal before the start of experimental therapy. "Seven patients had to stop the trial prematurely at either 60 or 80 minutes; three children (one each in groups 1, 2 and 3) stopped cooperating before the 120 minute measurement, and three children in group 2 and one child in group 3 were too ill to continue. Two patients had missing data at 80 minutes (because of vomiting) but both had recovered by 120 minutes"
Incomplete outcome data (attrition bias) All outcomes	Low risk	None identified
Selective reporting (reporting bias)	Low risk	None identified
Other bias	Low risk	

Sharma 2004

Methods	STUDY DESIGN: parallel LOCATION, NUMBER OF CENTERS: India, 1 center
Participants	N SCREENED: not available N RANDOMIZED: 50 N COMPLETED: 50 M = not available F = not available AGE: 6-14 years BASELINE DETAILS: % PEFR 34% (mean baseline of study population) INCLUSION CRITERIA: acute exacerbation of bronchial asthma defined as increasing cough, inability to speak in sentences and drink, wheezing and chest recession EXCLUSION CRITERIA: children with life-threatening or severe attack characterized by cyanosis, silent chest or poor air entry, marked dyspnoea so that a child was unable to speak even 3 or 4 words, PEFR < 30% for height, received bronchodilator 6 hours prior to admission, previous ITU admission
Interventions	PROTOCOL

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Sharma 2004 *(Continued)*

- Fixed: 60 minutes
- Observation period: 240 minutes
- Multiple fixed-dose protocol

INTERVENTION GROUP

- Salbutamol 0.03 mL/kg/dose (150 mcg/kg/dose) with 250 mcg IB q20 x 3

CONTROL GROUP

- Salbutamol 0.03 mL/kg/dose (150 mcg/kg/dose) q20 x 3

RUN-IN PERIOD

- None

CO-INTERVENTIONS

- Corticosteroids used in those who failed to respond

FOLLOW-UP

- 240 minutes

DEVICE

- Nebulizer

Outcomes	IMPROVEMENT IN % PREDICTED PEFR RESPIRATORY RATE WHEEZE SCORE USE OF ACCESSORY MUSCLES SCORES HOSPITAL ADMISSION RATE: reported ADMISSION RATE: not reported ADVERSE EVENTS
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	"The study was not blinded..."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed

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Sharma 2004 *(Continued)*

Selective reporting (reporting bias)	Low risk	None identified
Other bias	Low risk	None identified

Sienra Monge 2000

Methods	STUDY DESIGN: parallel LOCATION, NUMBER OF CENTERS: Children's Hospital of Mexico, Mexico DURATION OF STUDY: not available
Participants	N SCREENED: 40 N RANDOMIZED: 30 N COMPLETED: 30 M = 18 F = 12 AGE: 8-15 years BASELINE DETAILS: not available INCLUSION CRITERIA: acute asthma presenting to the emergency department (mild to severe according to the Woodran Scale) EXCLUSION CRITERIA: not available
Interventions	PROTOCOL • Fixed: 30 minutes • Observation period: 480 minutes • Multiple fixed-dose protocol INTERVENTION GROUP • Salbutamol 200 mcg + IB 120 mcg q10 minutes x 3 CONTROL GROUP • Salbutamol 200 mcg q10 minutes x 3 CO-INTERVENTION • Unclear FOLLOW-UP • 480 minutes DEVICE • MDI
Outcomes	CHANGE IN FEV_1 HOSPITALIZATION RATE

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Sienra Monge 2000 *(Continued)*

	ADMISSION CRITERIA: not reported
Notes	Translated by Luis Nannini

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	40 children referred to in the abstract but results are given for a study population of 30
Selective reporting (reporting bias)	Unclear risk	Unable to ascertain this
Other bias	Low risk	None identified

Watanasomsiri 2006

Methods	STUDY DESIGN: parallel LOCATION, NUMBER OF CENTERS: Thammasat University Hospital, Thailand DURATION OF STUDY: 2 years 5 months
Participants	N SCREENED: not available N RANDOMIZED: 74 N COMPLETED: 71 M = not available F = not available AGE: 3-15 years BASELINE DETAILS: % PEFR 29.2 (baseline characteristics of study group) INCLUSION CRITERIA: clinical diagnosis of asthma, moderate to severe asthma attack (children younger than 5 years were required to have 3 or more episodes of wheezing before the presenting illness) EXCLUSION CRITERIA: first-time episode of wheeze; co-existent cardiac, renal or other chronic pulmonary disease; bronchopulmonary dysplasia; intolerance to study drugs; glaucoma or urinary retention. Children who had used IP within 24 hours, used oral corticosteroids within 3 days and required immediate resuscitation or airway intervention were also excluded from the study
Interventions	PROTOCOL

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Watanasomsiri 2006 *(Continued)*

- Fixed 60 minutes
- Observation period 120 minutes
- Multiple fixed-dose protocol

INTERVENTION GROUP

- Salbutamol (1.2 mg for body weight < 10 kg and 2.5 mg for body weight > 10 kg) + 250 mcg of IB q20 minutes x 3

CONTROL GROUP

- Salbutamol (1.2 mg for body weight < 10 kg and 2.5 mg for body weight > 10 kg) + isotonic sodium chloride solution q20 minutes x 3

CO-INTERVENTIONS

- Oral corticosteroid 0.5 mg/kg with the second dose of the nebulized solution. After the third dose of the randomised medication, children received additional doses of nebulized salbutamol if indicated by incomplete clinical response at 70, 100 and 120 minutes

FOLLOW-UP PERIOD

- 3 days

DEVICE

- Nebulizer

Outcomes	CHANGE IN CLINICAL SCORE PULMONARY FUNCTION TESTS: % change in actual PEFR from baseline, changes in % predicted PEFR VITAL SIGNS: respiratory rate, heart rate, oxygen saturation NEED FOR ADDITIONAL SALBUTAMOL DOSES HOSPITALIZATION ADMISSION CRITERIA: not reported RELAPSE: within 3 days
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	Low risk	"Solutions supplied by pharmacy", "Solutions drawn up an independent nurse..."
Blinding (performance bias and detection bias) All outcomes	Low risk	"...parents and physicians were unaware of vial contents"
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 children withdrawn for technical reasons (errors in protocol) 1 child withdrawn by parents

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Watanasomsiri 2006 *(Continued)*

Selective reporting (reporting bias)	Low risk	None identified
Other bias	Low risk	None identified

Watson 1988

Methods	RANDOMIZATION: method and means not described BLINDING: double-blind, not described WITHDRAWAL/DROPOUT: none JADAD's QUALITY SCORE: 3
Participants	N: 31 AGE: 6-17 years BASELINE SEVERITY: 30-70% predicted FEV_1 COUNTRY: Canada OTHER: ability to perform spirometry consistently
Interventions	PROTOCOL • Fixed: 60 minutes • Observation period: 120 minutes total • Multiple fixed-dose protocol TEST GROUP • Fenoterol 625 mcg + IB 250 mcg combined q60 minutes x 2 CONTROL GROUP • Fenoterol 625 mcg q60 minutes x 2 CO-INTERVENTION • None FOLLOW-UP • 120 minutes DEVICE • Nebulizer
Outcomes	PULMONARY FUNCTION TESTS: change in % predicted FEV_1, % change in FEV_1 OXYGEN SATURATION: no details given CHANGE IN CLINICAL SCORE: pulmonary Index, no details given ADVERSE EFFECTS: tremor, "no adverse effects" but none other specified ADMISSION: described RELAPSE: not mentioned
Notes	
Risk of bias	

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Watson 1988 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, no other information available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Information not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Unclear risk	Unable to ascertain this reliably
Other bias	Low risk	None identified

Zorc 1999

Methods	STUDY DESIGN: parallel LOCATION, NUMBER OF CENTERS: John Hopkins Hospital, Baltimore, USA DURATION OF STUDY: 1 year
Participants	N SCREENED: 1215 N RANDOMIZED: 427 N COMPLETED: 427 M = 298 F = 129 AGE: 1-17 years BASELINE DETAILS: initial severity score of 1-3, excluded children if required initial therapy in addition to the critical pathway - initial severity score was incomplete/missing for 14% of the total 427 children of the full study INCLUSION CRITERIA: children who were to be treated according to a standardized emergency department protocol for acute asthma EXCLUSION CRITERIA: mild illness; decision not to treat on critical pathway; severe presentation requiring additional therapy; pretreatment with corticosteroids or IB; a history of glaucoma, CF or sickle cell disease
Interventions	PROTOCOL • Fixed: 60 minutes • Observation period: up to 295 minutes • Multiple fixed-dose protocol INTERVENTION GROUP

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Zorc 1999 *(Continued)*

	• Albuterol 2.5 mg (< 20 kg)/5.0 mg (≥ 20 kg) q20 minutes x 3 + IB 500 mcg at 20 and 40 minutes CONTROL GROUP • Albuterol 2.5 mg (< 20 kg)/5.0 mg (≥ 20 kg) q20 minutes x 3 + saline at 20 and 40 minutes CO-INTERVENTION (other medications used during the study) • Systemic corticosteroids: all received oral corticosteroids at 20 minutes FOLLOW-UP • 72 hours DEVICE • Nebulizer
Outcomes	# NEBULIZER TREATMENTS UNTIL DISPOSITION TIME TO DISPOSITION ADMISSION: to ward, to ICU ADMISSION CRITERIA: not reported RELAPSE
Notes	Author (MP) contacted Confirmation by MP of methodology and data extraction obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Number-coded solutions supplied by the pharmacy
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Trial protocol not reviewed
Other bias	Low risk	None identified

Zorc 1999 (mild)

Methods	STUDY DESIGN: parallel LOCATION, NUMBER OF CENTERS: John Hopkins Hospital, Baltimore, USA DURATION OF STUDY: 1 year

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Zorc 1999 (mild) *(Continued)*

Participants	N SCREENED: 1215 N RANDOMIZED: 427 N COMPLETED: 427 M = 298 F = 129 AGE: 1-17 years MILD GROUP N = 117 BASELINE DETAILS: initial severity score of 1-3, excluded children if required initial therapy in addition to the critical pathway - initial severity score was incomplete/missing for 14% of the total 427 children of the full study INCLUSION CRITERIA: children who were to be treated according to a standardized emergency department protocol for acute asthma EXCLUSION CRITERIA: mild illness; decision not to treat on critical pathway; severe presentation requiring additional therapy; pretreatment with corticosteroids or IB; a history of glaucoma, CF or sickle cell disease
Interventions	PROTOCOL • Fixed: 60 minutes • Observation period: up to 295 minutes • Multiple fixed-dose protocol INTERVENTION GROUP • Albuterol 2.5 mg (< 20 kg)/5.0 mg (≥ 20 kg) q20 minutes x 3 + IB 500 mcg at 20 and 40 minutes CONTROL GROUP • Albuterol 2.5 mg (< 20 kg)/5.0 mg (≥ 20 kg) q20 minutes x 3 + saline at 20 and 40 minutes CO-INTERVENTION (other medications used during the study) • Systemic corticosteroids: all received oral corticosteroids at 20 minutes FOLLOW-UP • 72 hours DEVICE • Nebulizer
Outcomes	# NEBULIZER TREATMENTS UNTIL DISPOSITION TIME TO DISPOSITION ADMISSION: to ward, to ICU ADMISSION CRITERIA: not reported RELAPSE
Notes	Author (MP) - contacted Confirmation by MP of methodology and data extraction obtained
Risk of bias	

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Zorc 1999 (mild) *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Number-coded solutions supplied by the pharmacy
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Trial protocol not reviewed
Other bias	Low risk	None identified

Zorc 1999 (moderate)

Methods	STUDY DESIGN: parallel LOCATION, NUMBER OF CENTERS: John Hopkins Hospital, Baltimore, USA DURATION OF STUDY: 1 year
Participants	N SCREENED: 1215 N RANDOMIZED: 427 N COMPLETED: 427 M = 298 F = 129 AGE: 1-17 years MODERATE GROUP: N = 194 BASELINE DETAILS: initial severity score of 4-6, excluded if required initial therapy in addition to the critical pathway - initial severity score was incomplete/missing for 14% of the total 427 children of the full study INCLUSION CRITERIA: children who were to be treated according to a standardized emergency department protocol for acute asthma EXCLUSION CRITERIA: mild illness; decision not to treat on critical pathway; severe presentation requiring additional therapy; pretreatment with corticosteroids or IB; a history of glaucoma, CF or sickle cell disease
Interventions	PROTOCOL • Fixed: 60 minutes • Observation period: up to 295 minutes • Multiple fixed-dose protocol

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Zorc 1999 (moderate) *(Continued)*

	INTERVENTION GROUP • Albuterol 2.5 mg (< 20 kg)/5.0 mg (≥ 20 kg) q20 minutes x 3 + IB 500 mcg at 20 and 40 minutes CONTROL GROUP • Albuterol 2.5 mg (< 20 kg)/5.0 mg (≥ 20 kg) q20 minutes x 3 + saline at 20 and 40 minutes CO-INTERVENTION (other medications used during the study) • Systemic corticosteroids : all received oral corticosteroids at 20 minutes FOLLOW-UP • 72 hours DEVICE • Nebulizer
Outcomes	# NEBULIZER TREATMENTS UNTIL DISPOSITION TIME TO DISPOSITION ADMISSION: to ward, to ICU ADMISSION CRITERIA: not reported RELAPSE
Notes	Author (MP) contacted Confirmation by MP of methodology and data extraction obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Number-coded solutions supplied by the pharmacy
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Trial protocol not reviewed
Other bias	Low risk	None identified

Zorc 1999 (severe)

Methods	STUDY DESIGN: Parallel LOCATION, NUMBER OF CENTERS: John Hopkins Hospital, Baltimore, USA

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Zorc 1999 (severe) *(Continued)*

	DURATION OF STUDY: 1 year
Participants	N SCREENED: 1215 N RANDOMIZED: 427 N COMPLETED: 427 M = 298 F = 129 AGE: 1-17 years SEVERE GROUP: N = 51 BASELINE DETAILS: initial severity score of 7-9, excluded children if respiratory failure or required initial therapy in addition to the critical pathway - initial severity score was incomplete/missing for 14% of the total 427 children of the full study INCLUSION CRITERIA: children who were to be treated according to a standardized emergency department protocol for acute asthma EXCLUSION CRITERIA: mild illness; decision not to treat on critical pathway; severe presentation requiring additional therapy; pretreatment with corticosteroids or IB; a history of glaucoma, CF or sickle cell disease
Interventions	PROTOCOL • Fixed: 60 minutes • Observation period: up to 295 minutes • Multiple fixed-dose protocol INTERVENTION GROUP • Albuterol 2.5 mg (< 20 kg)/5.0 mg (≥ 20 kg) q20 minutes x 3 + IB 500 mcg at 20 and 40 minutes CONTROL GROUP • Albuterol 2.5 mg (< 20 kg)/5.0 mg (≥ 20 kg) q20 minutes x 3 + saline at 20 and 40 minutes CO-INTERVENTION (other medications used during the study) • Systemic corticosteroids: all received oral corticosteroids at 20 minutes FOLLOW-UP • 72 hours DEVICE • Nebulizer
Outcomes	# NEBULIZER TREATMENTS UNTIL DISPOSITION TIME TO DISPOSITION ADMISSION: to ward, to ICU ADMISSION CRITERIA: not reported RELAPSE
Notes	Author (MP) contacted Confirmation by MP of methodology and data extraction obtained

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Zorc 1999 (severe) *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Number-coded solutions supplied by the pharmacy
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Trial protocol not reviewed
Other bias	Low risk	None identified

CF: cystic fibrosis; F: female; FEF: forced expiratory flow; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; IB: ipratropium bromide; ICU: intensive care unit; ITU: intensive therapy unit; M: male; MDI: metered-dose inhaler; PEF: peak expiratory flow; PEFR: peak expiratory flow rate; PICU: paediatric intensive care unit; q: over (e.g. q15 means over 15 minutes); UDV: unit dose vial; y.o.: years old.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Anthracopoulos 2005	Study compared anticholinergic agents and salbutamol versus higher dose of salbutamol alone
Boner 1987	Study on people with stable asthma
Bratteby 1986	Study on people with chronic asthma
Browne 2002	Hospitalized participants treated with IV salbutamol and placebo versus IV salbutamol and anticholinergics
Caubet 1989	Study on people with chronic asthma
Craven 2001	Acute inpatient setting
Davis 1984	Study on people with stable asthma
Delacourt 1994	The study was not a randomised controlled trial
DeStefano 1989	Study on people with chronic asthma
Ekwo 1978	The study was not a randomised controlled trial
Freeman 1989	The study pertained to participants who were already admitted

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Study	Reason for exclusion
Friberg 1989	Study on people with chronic asthma
Goggin 2001	Hospitalized children
Greenough 1986	Study on people with chronic asthma
Groggins 1981	Study on people with stable asthma
Hodges 1981	The study pertained to infants
Kumaratne 2003	Significant number of participants under 18 months (mean: 19-27 months, SD 20-23)
Lenney 1986	Study on people with chronic asthma
Mann 1982	Study on people with chronic asthma
O'Driscoll 1989	Age range: 17-81 years
Paredes 1994	Conference abstract - incomplete data given
Ralston 2005	Different SABAs used in each treatment arm
Rayner 1987	The study pertained to people who were already admitted
Stokes 1983	The study did not combine anticholinergic inhalations and SABAs inhalations
Storr 1986	The study pertained to people who were already admitted
Timsit 2002	Different doses of SABA in treatment groups
Vichyanond 1990	Study on people with chronic asthma
Ward 1981	Age range: 15-79 year olds
Ward 1985	Age range: 14-75 years
Wilson 1984	Study on people with chronic asthma

IV: intravenous; SABA: short-acting beta-agonists; SD: standard deviation.

DATA AND ANALYSES

Comparison 1. Anticholinergic and beta$_2$-agonists versus beta$_2$-agonists alone (all protocols)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary outcome: hospital admissions	19	2497	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.63, 0.85]
2 Primary outcome: hospital admissions subgrouped by trial protocol	19	2497	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.63, 0.85]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Single-dose protocol	3	419	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.56, 1.26]
2.2 Multiple fixed-dose protocol	15	1998	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.61, 0.84]
2.3 Multiple flexible-dose protocol	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Primary outcome: hospital admissions subgrouped by review authors' judgment of trial report	18	2497	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.63, 0.85]
3.1 Severe	8	1188	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.61, 0.87]
3.2 Moderate-severe	4	371	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.41, 0.89]
3.3 Moderate	3	463	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.49, 1.22]
3.4 Mild-moderate	2	358	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.52, 1.47]
3.5 Mild	1	117	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.42, 4.79]
4 Primary outcome: hospital admissions subgrouped by control group event rate (tertiles)	18	2417	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.63, 0.85]
4.1 High control group event rate (upper tertile)	6	669	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.56, 0.82]
4.2 Medium control group event rate (middle tertile)	6	780	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.57, 0.99]
4.3 Low control group event rate (lower tertile)	6	968	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.59, 1.42]
5 Primary outcome: hospital admissions subgrouped by co-intervention of corticosteroid	17	2407	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.63, 0.84]
5.1 Background corticosteroids	8	1043	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.59, 0.86]
5.2 No background corticosteroids	6	353	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.47, 0.94]
5.3 Variable (at physicians discretion)	3	511	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.54, 1.10]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.4 Not reported	1	500	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.48, 1.53]
6 Change from baseline in % predicted FEV_1, 60 minutes after the last of IB	5	402	Mean Difference (IV, Fixed, 95% CI)	10.08 [6.24, 13.92]
7 Change from baseline in % predicted FEV_1, 120 minutes after last IB	2	117	Mean Difference (IV, Fixed, 95% CI)	6.87 [1.17, 12.56]
8 % Change in FEV_1 or PEFR at 60 minutes after last IB (± 15 minutes)	4	166	Std. Mean Difference (IV, Fixed, 95% CI)	0.57 [0.25, 0.88]
9 % Change in FEV_1 or PEFR at 120 minutes after last IB (± 30 minutes)	4	219	Std. Mean Difference (IV, Fixed, 95% CI)	0.12 [-0.15, 0.39]
10 % Change in respiratory resistance at 60 minutes after IB (± 15 minutes)	1	294	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.02, 0.07]
10.1 Co-intervention: corticosteroids during the previous 60 minutes	1	70	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.13, 0.09]
10.2 Co-intervention: no corticosteroids	1	224	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.02, 0.08]
11 % Change in respiratory resistance at 120 minutes after IB (± 30 minutes)	1	108	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.09, 0.07]
11.1 Co-intervention: corticosteroids during the previous 120 minutes	1	47	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.12, 0.16]
11.2 Co-intervention: no corticosteroids	1	61	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.12, 0.08]
12 Change in clinical score at 120 minutes (± 30 minutes)	3	934	Std. Mean Difference (IV, Fixed, 95% CI)	-0.23 [-0.42, -0.04]
13 Need for repeat bronchodilator treatment after standard protocol prior to disposition	9	1074	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.79, 0.97]
14 O_2 saturation < 95% at 60 minutes (± 15 minutes)	2	416	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.55, 0.97]
15 O_2 saturation < 95% at 120 minutes (± 30 minutes)	2	185	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.76, 1.59]
16 Need for corticosteroids in emergency department prior to disposition	2	378	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.73, 1.08]
17 Tremor	9	524	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.51, 0.93]
18 Vomiting	8	1230	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.49, 1.56]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19 Nausea	7	757	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.38, 0.95]
20 Relapse	10	1389	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.68, 1.68]

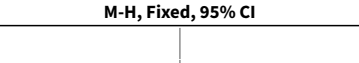
Analysis 1.1. Comparison 1 Anticholinergic and beta$_2$-agonists versus beta$_2$-agonists alone (all protocols), Outcome 1 Primary outcome: hospital admissions.

Study or subgroup	Anticholinergic + SABA n/N	SABA n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Benito Fernandez 2000	18/51	27/51		9.29%	0.67[0.42,1.05]
BI [pers comm]	19/246	23/254		7.79%	0.85[0.48,1.53]
Calvo 1998	0/40	0/40			Not estimable
Chakraborti 2006	0/30	0/30			Not estimable
Ducharme 1998	23/156	24/142		8.64%	0.87[0.52,1.47]
Iramain 2011	9/53	21/53		7.22%	0.43[0.22,0.85]
Peterson 1996	19/82	25/81		8.65%	0.75[0.45,1.25]
Qureshi 1997	9/36	14/31		5.18%	0.55[0.28,1.1]
Qureshi 1998 (moderate)	8/91	9/98		2.98%	0.96[0.39,2.37]
Qureshi 1998 (severe)	51/137	71/136		24.52%	0.71[0.54,0.93]
Reisman 1988	2/11	3/13		0.95%	0.79[0.16,3.9]
Schuh 1995 (multiple)	17/40	9/20		4.13%	0.94[0.52,1.73]
Schuh 1995 (single)	15/40	10/21		4.51%	0.79[0.43,1.44]
Sharma 2004	1/25	4/25		1.38%	0.25[0.03,2.08]
Watanasomsiri 2006	2/38	3/33		1.1%	0.58[0.1,3.26]
Watson 1988	0/16	0/15			Not estimable
Zorc 1999 (mild)	6/60	4/57		1.41%	1.43[0.42,4.79]
Zorc 1999 (moderate)	18/98	25/96		8.69%	0.71[0.41,1.21]
Zorc 1999 (severe)	7/22	12/29		3.56%	0.77[0.36,1.63]
Total (95% CI)	**1272**	**1225**		**100%**	**0.73[0.63,0.85]**
Total events: 224 (Anticholinergic + SABA), 284 (SABA)					
Heterogeneity: Tau^2=0; Chi^2=7.25, df=15(P=0.95); I^2=0%					
Test for overall effect: Z=4.13(P<0.0001)					

Favours Anticholinergic + SABA — Favours SABA

Analysis 1.2. Comparison 1 Anticholinergic and beta$_2$-agonists versus beta$_2$-agonists alone (all protocols), Outcome 2 Primary outcome: hospital admissions subgrouped by trial protocol.

Study or subgroup	Anticholinergic + SABA n/N	SABA n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Single-dose protocol					
Schuh 1995 (single)	15/40	10/21		4.51%	0.79[0.43,1.44]



Favours Anticholinergic + SABA — Favours SABA

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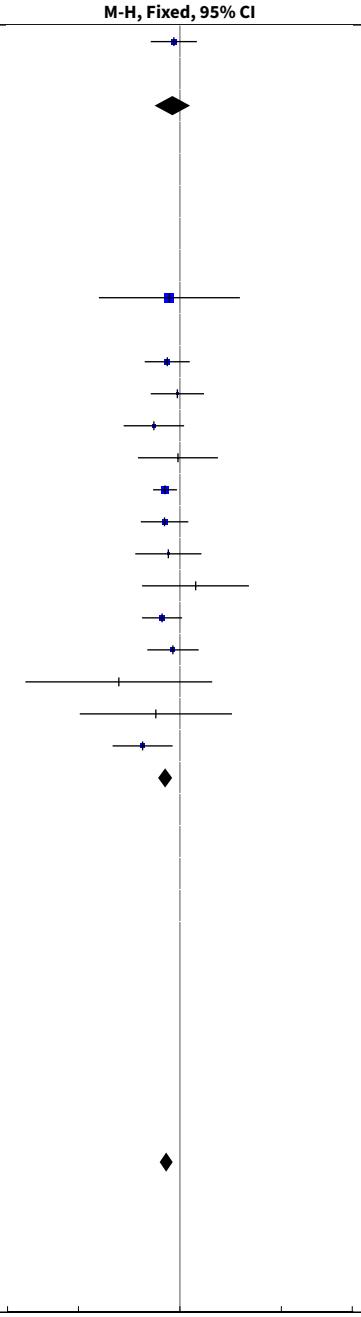
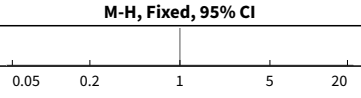
Study or subgroup	Anticholinergic + SABA n/N	SABA n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ducharme 1998	23/156	24/142		8.64%	0.87[0.52,1.47]
Chakraborti 2006	0/30	0/30			Not estimable
Subtotal (95% CI)	**226**	**193**		**13.16%**	**0.84[0.56,1.26]**
Total events: 38 (Anticholinergic + SABA), 34 (SABA)					
Heterogeneity: Tau^2=0; Chi^2=0.07, df=1(P=0.8); I^2=0%					
Test for overall effect: Z=0.83(P=0.41)					
1.2.2 Multiple fixed-dose protocol					
Reisman 1988	2/11	3/13		0.95%	0.79[0.16,3.9]
Watson 1988	0/16	0/15			Not estimable
Peterson 1996	19/82	25/81		8.65%	0.75[0.45,1.25]
Schuh 1995 (multiple)	17/40	9/20		4.13%	0.94[0.52,1.73]
Qureshi 1997	9/36	14/31		5.18%	0.55[0.28,1.1]
Qureshi 1998 (moderate)	8/91	9/98		2.98%	0.96[0.39,2.37]
Qureshi 1998 (severe)	51/137	71/136		24.52%	0.71[0.54,0.93]
Zorc 1999 (moderate)	18/98	25/96		8.69%	0.71[0.41,1.21]
Zorc 1999 (severe)	7/22	12/29		3.56%	0.77[0.36,1.63]
Zorc 1999 (mild)	6/60	4/57		1.41%	1.43[0.42,4.79]
Benito Fernandez 2000	18/51	27/51		9.29%	0.67[0.42,1.05]
BI [pers comm]	19/246	23/254		7.79%	0.85[0.48,1.53]
Sharma 2004	1/25	4/25		1.38%	0.25[0.03,2.08]
Watanasomsiri 2006	2/38	3/33		1.1%	0.58[0.1,3.26]
Iramain 2011	9/53	21/53		7.22%	0.43[0.22,0.85]
Subtotal (95% CI)	**1006**	**992**		**86.84%**	**0.72[0.61,0.84]**
Total events: 186 (Anticholinergic + SABA), 250 (SABA)					
Heterogeneity: Tau^2=0; Chi^2=6.69, df=13(P=0.92); I^2=0%					
Test for overall effect: Z=4.12(P<0.0001)					
1.2.3 Multiple flexible-dose protocol					
Calvo 1998	0/40	0/40			Not estimable
Subtotal (95% CI)	**40**	**40**			**Not estimable**
Total events: 0 (Anticholinergic + SABA), 0 (SABA)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**1272**	**1225**		**100%**	**0.73[0.63,0.85]**
Total events: 224 (Anticholinergic + SABA), 284 (SABA)					
Heterogeneity: Tau^2=0; Chi^2=7.25, df=15(P=0.95); I^2=0%					
Test for overall effect: Z=4.13(P<0.0001)					
Test for subgroup differences: Chi^2=0.55, df=1 (P=0.46), I^2=0%					



Analysis 1.3. Comparison 1 Anticholinergic and beta$_2$-agonists versus beta$_2$-agonists alone (all protocols), Outcome 3 Primary outcome: hospital admissions subgrouped by review authors' judgment of trial report.

Study or subgroup	Anticholinergic + SABA n/N	SABA n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Severe					



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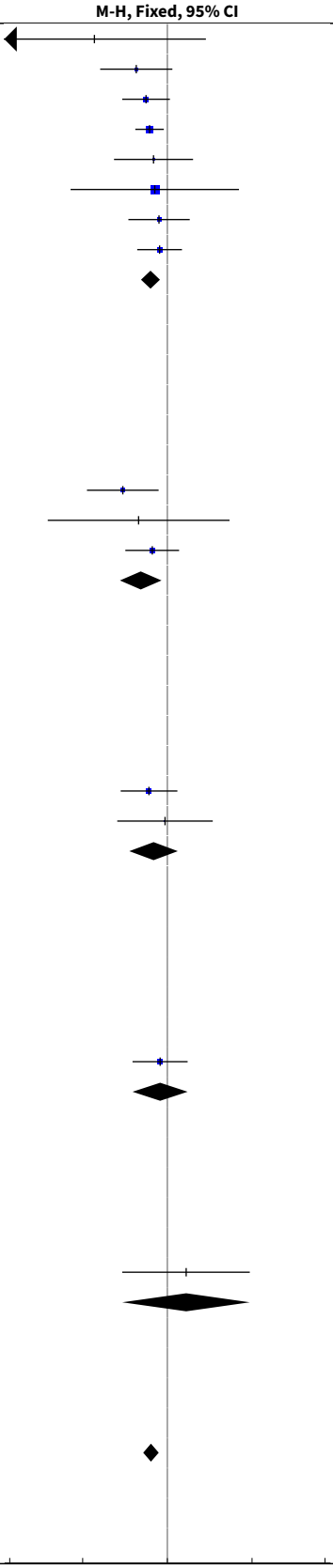
Study or subgroup	Anticholinergic + SABA n/N	SABA n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Sharma 2004	1/25	4/25		1.38%	0.25[0.03,2.08]
Qureshi 1997	9/36	14/31		5.18%	0.55[0.28,1.1]
Benito Fernandez 2000	18/51	27/51		9.29%	0.67[0.42,1.05]
Qureshi 1998 (severe)	51/137	71/136		24.51%	0.71[0.54,0.93]
Zorc 1999 (severe)	7/22	12/29		3.56%	0.77[0.36,1.63]
Reisman 1988	2/11	3/13		0.95%	0.79[0.16,3.9]
BI [pers comm]	19/246	23/254		7.79%	0.85[0.48,1.53]
Schuh 1995	32/80	19/41		8.64%	0.86[0.56,1.32]
Subtotal (95% CI)	**608**	**580**		**61.29%**	**0.73[0.61,0.87]**
Total events: 139 (Anticholinergic + SABA), 173 (SABA)					
Heterogeneity: Tau^2=0; Chi^2=2.69, df=7(P=0.91); I^2=0%					
Test for overall effect: Z=3.49(P=0)					
1.3.2 Moderate-severe					
Watson 1988	0/16	0/15			Not estimable
Iramain 2011	9/53	21/53		7.22%	0.43[0.22,0.85]
Watanasomsiri 2006	2/38	3/33		1.1%	0.58[0.1,3.26]
Peterson 1996	19/82	25/81		8.65%	0.75[0.45,1.25]
Subtotal (95% CI)	**189**	**182**		**16.98%**	**0.6[0.41,0.89]**
Total events: 30 (Anticholinergic + SABA), 49 (SABA)					
Heterogeneity: Tau^2=0; Chi^2=1.67, df=2(P=0.43); I^2=0%					
Test for overall effect: Z=2.51(P=0.01)					
1.3.3 Moderate					
Calvo 1998	0/40	0/40			Not estimable
Zorc 1999 (moderate)	18/98	25/96		8.69%	0.71[0.41,1.21]
Qureshi 1998 (moderate)	8/91	9/98		2.98%	0.96[0.39,2.37]
Subtotal (95% CI)	**229**	**234**		**11.67%**	**0.77[0.49,1.22]**
Total events: 26 (Anticholinergic + SABA), 34 (SABA)					
Heterogeneity: Tau^2=0; Chi^2=0.32, df=1(P=0.57); I^2=0%					
Test for overall effect: Z=1.11(P=0.27)					
1.3.4 Mild-moderate					
Chakraborti 2006	0/30	0/30			Not estimable
Ducharme 1998	23/156	24/142		8.64%	0.87[0.52,1.47]
Subtotal (95% CI)	**186**	**172**		**8.64%**	**0.87[0.52,1.47]**
Total events: 23 (Anticholinergic + SABA), 24 (SABA)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.51(P=0.61)					
1.3.5 Mild					
Zorc 1999 (mild)	6/60	4/57		1.41%	1.43[0.42,4.79]
Subtotal (95% CI)	**60**	**57**		**1.41%**	**1.43[0.42,4.79]**
Total events: 6 (Anticholinergic + SABA), 4 (SABA)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.57(P=0.57)					
Total (95% CI)	**1272**	**1225**		**100%**	**0.73[0.63,0.85]**
Total events: 224 (Anticholinergic + SABA), 284 (SABA)					
Heterogeneity: Tau^2=0; Chi^2=7.08, df=14(P=0.93); I^2=0%					
Test for overall effect: Z=4.13(P<0.0001)					



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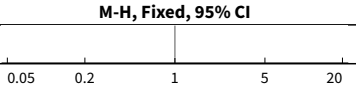
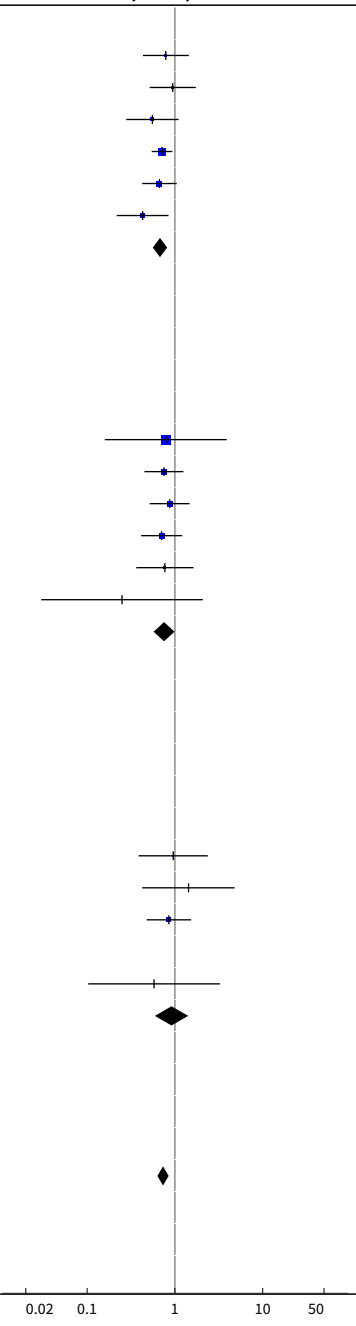
Study or subgroup	Anticholinergic + SABA n/N	SABA n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for subgroup differences: Chi²=2.57, df=1 (P=0.63), I²=0%					



Analysis 1.4. Comparison 1 Anticholinergic and beta$_2$-agonists versus beta$_2$-agonists alone (all protocols), Outcome 4 Primary outcome: hospital admissions subgrouped by control group event rate (tertiles).

Study or subgroup	Anticholinergic + SABA n/N	SABA n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 High control group event rate (upper tertile)					
Schuh 1995 (single)	15/40	10/21		4.51%	0.79[0.43,1.44]
Schuh 1995 (multiple)	17/40	9/20		4.13%	0.94[0.52,1.73]
Qureshi 1997	9/36	14/31		5.18%	0.55[0.28,1.1]
Qureshi 1998 (severe)	51/137	71/136		24.52%	0.71[0.54,0.93]
Benito Fernandez 2000	18/51	27/51		9.29%	0.67[0.42,1.05]
Iramain 2011	9/53	21/53		7.22%	0.43[0.22,0.85]
Subtotal (95% CI)	**357**	**312**		**54.84%**	**0.68[0.56,0.82]**
Total events: 119 (Anticholinergic + SABA), 152 (SABA)					
Heterogeneity: Tau²=0; Chi²=3.62, df=5(P=0.61); I²=0%					
Test for overall effect: Z=4.07(P<0.0001)					
1.4.2 Medium control group event rate (middle tertile)					
Reisman 1988	2/11	3/13		0.95%	0.79[0.16,3.9]
Peterson 1996	19/82	25/81		8.65%	0.75[0.45,1.25]
Ducharme 1998	23/156	24/142		8.64%	0.87[0.52,1.47]
Zorc 1999 (moderate)	18/98	25/96		8.69%	0.71[0.41,1.21]
Zorc 1999 (severe)	7/22	12/29		3.56%	0.77[0.36,1.63]
Sharma 2004	1/25	4/25		1.38%	0.25[0.03,2.08]
Subtotal (95% CI)	**394**	**386**		**31.87%**	**0.75[0.57,0.99]**
Total events: 70 (Anticholinergic + SABA), 93 (SABA)					
Heterogeneity: Tau²=0; Chi²=1.4, df=5(P=0.92); I²=0%					
Test for overall effect: Z=2.03(P=0.04)					
1.4.3 Low control group event rate (lower tertile)					
Watson 1988	0/16	0/15			Not estimable
Qureshi 1998 (moderate)	8/91	9/98		2.98%	0.96[0.39,2.37]
Zorc 1999 (mild)	6/60	4/57		1.41%	1.43[0.42,4.79]
BI [pers comm]	19/246	23/254		7.79%	0.85[0.48,1.53]
Chakraborti 2006	0/30	0/30			Not estimable
Watanasomsiri 2006	2/38	3/33		1.1%	0.58[0.1,3.26]
Subtotal (95% CI)	**481**	**487**		**13.28%**	**0.91[0.59,1.42]**
Total events: 35 (Anticholinergic + SABA), 39 (SABA)					
Heterogeneity: Tau²=0; Chi²=0.85, df=3(P=0.84); I²=0%					
Test for overall effect: Z=0.4(P=0.69)					
Total (95% CI)	**1232**	**1185**		**100%**	**0.73[0.63,0.85]**
Total events: 224 (Anticholinergic + SABA), 284 (SABA)					
Heterogeneity: Tau²=0; Chi²=7.25, df=15(P=0.95); I²=0%					
Test for overall effect: Z=4.13(P<0.0001)					



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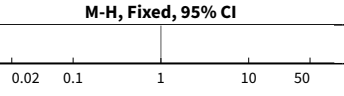
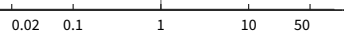
Study or subgroup	Anticholinergic + SABA n/N	SABA n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for subgroup differences: Chi²=1.68, df=1 (P=0.43), I²=0%					



Analysis 1.5. Comparison 1 Anticholinergic and beta$_2$-agonists versus beta$_2$-agonists alone (all protocols), Outcome 5 Primary outcome: hospital admissions subgrouped by co-intervention of corticosteroid.

Study or subgroup	Anticholinergic + SABA n/N	SABA n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.5.1 Background corticosteroids					
Qureshi 1997	9/36	14/31		5.11%	0.55[0.28,1.1]
Qureshi 1998 (severe)	51/137	71/136		24.18%	0.71[0.54,0.93]
Qureshi 1998 (moderate)	8/91	9/98		2.94%	0.96[0.39,2.37]
Zorc 1999 (mild)	6/60	4/57		1.39%	1.43[0.42,4.79]
Zorc 1999 (moderate)	18/98	25/96		8.57%	0.71[0.41,1.21]
Zorc 1999 (severe)	7/22	12/29		3.51%	0.77[0.36,1.63]
Benito Fernandez 2000	18/51	27/51		9.16%	0.67[0.42,1.05]
Sharma 2004	1/25	4/25		1.36%	0.25[0.03,2.08]
Subtotal (95% CI)	**520**	**523**		**56.23%**	**0.71[0.59,0.86]**
Total events: 118 (Anticholinergic + SABA), 166 (SABA)					
Heterogeneity: Tau²=0; Chi²=3.24, df=7(P=0.86); I²=0%					
Test for overall effect: Z=3.48(P=0)					
1.5.2 No background corticosteroids					
Reisman 1988	2/11	3/13		0.93%	0.79[0.16,3.9]
Watson 1988	0/16	0/15			Not estimable
Schuh 1995 (single)	15/40	10/21		4.45%	0.79[0.43,1.44]
Schuh 1995 (multiple)	17/40	9/20		4.07%	0.94[0.52,1.73]
Watanasomsiri 2006	2/38	3/33		1.09%	0.58[0.1,3.26]
Iramain 2011	9/53	21/53		7.13%	0.43[0.22,0.85]
Subtotal (95% CI)	**198**	**155**		**17.67%**	**0.67[0.47,0.94]**
Total events: 45 (Anticholinergic + SABA), 46 (SABA)					
Heterogeneity: Tau²=0; Chi²=3.26, df=4(P=0.52); I²=0%					
Test for overall effect: Z=2.29(P=0.02)					
1.5.3 Variable (at physicians discretion)					
Peterson 1996	19/82	25/81		8.54%	0.75[0.45,1.25]
Ducharme 1998	23/156	24/142		8.53%	0.87[0.52,1.47]
Sharma 2004	1/25	4/25		1.36%	0.25[0.03,2.08]
Subtotal (95% CI)	**263**	**248**		**18.42%**	**0.77[0.54,1.1]**
Total events: 43 (Anticholinergic + SABA), 53 (SABA)					
Heterogeneity: Tau²=0; Chi²=1.31, df=2(P=0.52); I²=0%					
Test for overall effect: Z=1.42(P=0.15)					
1.5.4 Not reported					
BI [pers comm]	19/246	23/254		7.68%	0.85[0.48,1.53]
Subtotal (95% CI)	**246**	**254**		**7.68%**	**0.85[0.48,1.53]**
Total events: 19 (Anticholinergic + SABA), 23 (SABA)					
Heterogeneity: Not applicable					



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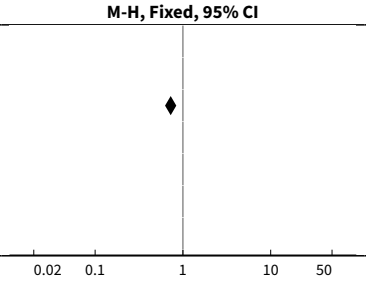
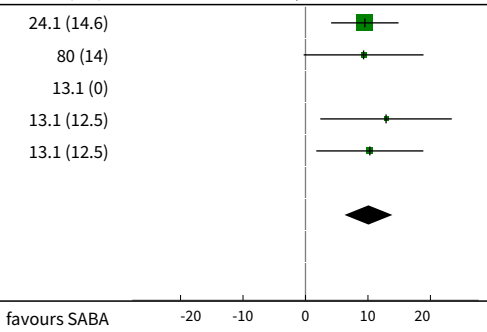
Study or subgroup	Anticholinergic + SABA n/N	SABA n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: Z=0.54(P=0.59)					
Total (95% CI)	**1227**	**1180**		**100%**	**0.73[0.63,0.84]**
Total events: 225 (Anticholinergic + SABA), 288 (SABA)					
Heterogeneity: Tau²=0; Chi²=8.23, df=16(P=0.94); I²=0%					
Test for overall effect: Z=4.26(P<0.0001)					
Test for subgroup differences: Chi²=0.66, df=1 (P=0.88), I²=0%					



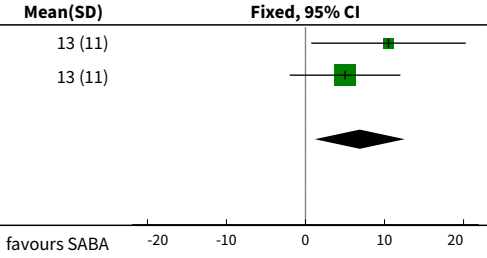
Analysis 1.6. Comparison 1 Anticholinergic and beta$_2$-agonists versus beta$_2$-agonists alone (all protocols), Outcome 6 Change from baseline in % predicted FEV$_1$, 60 minutes after the last of IB.

Study or subgroup	Anticholinergic + SABA N	Anticholinergic + SABA Mean(SD)	SABA N	SABA Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Qureshi 1997	45	33.6 (11.3)	45	24.1 (14.6)		50.63%	9.5[4.11,14.89]
Watson 1988	16	89.3 (13.2)	15	80 (14)		16.01%	9.3[-0.29,18.89]
Peterson 1996	82	14.7 (0)	81	13.1 (0)			Not estimable
Schuh 1995 (multiple)	40	26 (29)	20	13.1 (12.5)		13.3%	12.9[2.37,23.43]
Schuh 1995 (single)	39	23.4 (20.6)	19	13.1 (12.5)		20.07%	10.3[1.73,18.87]
Total ***	**222**		**180**			**100%**	**10.08[6.24,13.92]**
Heterogeneity: Tau²=0; Chi²=0.35, df=3(P=0.95); I²=0%							
Test for overall effect: Z=5.15(P<0.0001)							



Analysis 1.7. Comparison 1 Anticholinergic and beta$_2$-agonists versus beta$_2$-agonists alone (all protocols), Outcome 7 Change from baseline in % predicted FEV$_1$, 120 minutes after last IB.

Study or subgroup	Anticholinergic + SABA N	Anticholinergic + SABA Mean(SD)	SABA N	SABA Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Schuh 1995 (multiple)	40	23.5 (27.2)	19	13 (11)		33.93%	10.5[0.73,20.27]
Schuh 1995 (single)	39	18 (15.8)	19	13 (11)		66.07%	5[-2,12]
Total ***	**79**		**38**			**100%**	**6.87[1.17,12.56]**
Heterogeneity: Tau²=0; Chi²=0.8, df=1(P=0.37); I²=0%							
Test for overall effect: Z=2.36(P=0.02)							



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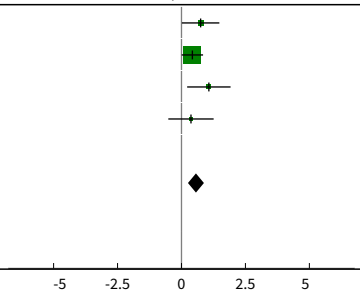
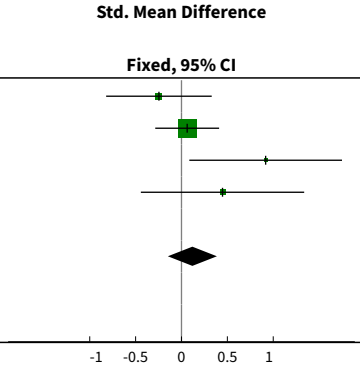
Analysis 1.8. Comparison 1 Anticholinergic and beta$_2$-agonists versus beta$_2$-agonists alone (all protocols), Outcome 8 % Change in FEV$_1$ or PEFR at 60 minutes after last IB (± 15 minutes).

Study or subgroup	Anticholinergic + SABA N	Anticholinergic + SABA Mean(SD)	SABA N	SABA Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Watson 1988	16	63.6 (28.4)	15	42.1 (27.5)		18.2%	0.75[0.02,1.48]
Qureshi 1997	45	32.6 (11.7)	45	26.8 (15.1)		55.82%	0.43[0.01,0.84]
Beck 1985	13	20.4 (19.5)	12	4.1 (6.2)		13.55%	1.07[0.22,1.92]
Phanichyakam 1990	10	36.4 (36)	10	22 (38.3)		12.43%	0.37[-0.51,1.26]
Total ***	**84**		**82**			**100%**	**0.57[0.25,0.88]**
Heterogeneity: Tau^2=0; Chi^2=2.22, df=3(P=0.53); I^2=0%							
Test for overall effect: Z=3.55(P=0)							



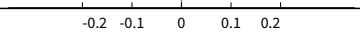
Analysis 1.9. Comparison 1 Anticholinergic and beta$_2$-agonists versus beta$_2$-agonists alone (all protocols), Outcome 9 % Change in FEV$_1$ or PEFR at 120 minutes after last IB (± 30 minutes).

Study or subgroup	Anticholinergic + SABA N	Anticholinergic + SABA Mean(SD)	SABA N	SABA Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Qureshi 1998 (moderate)	22	26 (12)	25	29 (12)		21.61%	-0.25[-0.82,0.33]
Qureshi 1998 (severe)	65	32 (15)	62	31 (17)		59.04%	0.06[-0.29,0.41]
Beck 1985	13	21.1 (22.7)	12	3.2 (13.5)		10.33%	0.92[0.09,1.75]
Phanichyakam 1990	10	34.3 (25)	10	18.5 (40.8)		9.03%	0.45[-0.44,1.34]
Total ***	**110**		**109**			**100%**	**0.12[-0.15,0.39]**
Heterogeneity: Tau^2=0; Chi^2=5.71, df=3(P=0.13); I^2=47.43%							
Test for overall effect: Z=0.87(P=0.38)							



Analysis 1.10. Comparison 1 Anticholinergic and beta$_2$-agonists versus beta$_2$-agonists alone (all protocols), Outcome 10 % Change in respiratory resistance at 60 minutes after IB (± 15 minutes).

Study or subgroup	Anticholinergic + SABA N	Anticholinergic + SABA Mean(SD)	SABA N	SABA Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.10.1 Co-intervention: corticosteroids during the previous 60 minutes							
Ducharme 1998	31	-0.3 (0.3)	39	-0.3 (0.2)		14.87%	-0.02[-0.13,0.09]
Subtotal ***	**31**		**39**			**14.87%**	**-0.02[-0.13,0.09]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.35(P=0.73)							
1.10.2 Co-intervention: no corticosteroids							
Ducharme 1998	124	-0.3 (0.2)	100	-0.3 (0.2)		85.13%	0.03[-0.02,0.08]
Subtotal ***	**124**		**100**			**85.13%**	**0.03[-0.02,0.08]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.25(P=0.21)							



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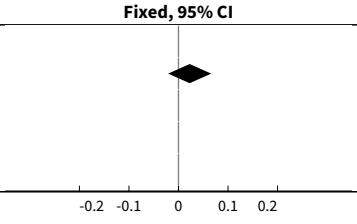
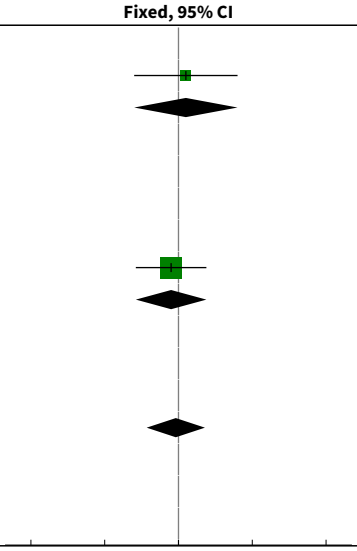
Study or subgroup	Anticholinergic + SABA N	Anticholinergic + SABA Mean(SD)	SABA N	SABA Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Total ***	**155**		**139**			**100%**	**0.02[-0.02,0.07]**
Heterogeneity: Tau²=0; Chi²=0.64, df=1(P=0.42); I²=0%							
Test for overall effect: Z=1.02(P=0.31)							
Test for subgroup differences: Chi²=0.64, df=1 (P=0.42), I²=0%							



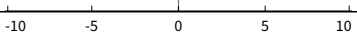
Analysis 1.11. Comparison 1 Anticholinergic and beta$_2$-agonists versus beta$_2$-agonists alone (all protocols), Outcome 11 % Change in respiratory resistance at 120 minutes after IB (± 30 minutes).

Study or subgroup	Anticholinergic + SABA N	Anticholinergic + SABA Mean(SD)	SABA N	SABA Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.11.1 Co-intervention: corticosteroids during the previous 120 minutes							
Ducharme 1998	22	-0.3 (0.2)	25	-0.3 (0.3)		31.79%	0.02[-0.12,0.16]
Subtotal ***	**22**		**25**			**31.79%**	**0.02[-0.12,0.16]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.28(P=0.78)							
1.11.2 Co-intervention: no corticosteroids							
Ducharme 1998	36	-0.3 (0.2)	25	-0.3 (0.2)		68.21%	-0.02[-0.12,0.08]
Subtotal ***	**36**		**25**			**68.21%**	**-0.02[-0.12,0.08]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.41(P=0.68)							
Total ***	**58**		**50**			**100%**	**-0.01[-0.09,0.07]**
Heterogeneity: Tau²=0; Chi²=0.21, df=1(P=0.64); I²=0%							
Test for overall effect: Z=0.18(P=0.86)							
Test for subgroup differences: Chi²=0.21, df=1 (P=0.64), I²=0%							



Analysis 1.12. Comparison 1 Anticholinergic and beta$_2$-agonists versus beta$_2$-agonists alone (all protocols), Outcome 12 Change in clinical score at 120 minutes (± 30 minutes).

Study or subgroup	Anticholinergic + SABA N	Anticholinergic + SABA Mean(SD)	SABA N	SABA Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Qureshi 1998 (moderate)	79	-3.9 (1.2)	84	-3.6 (1.3)		37.51%	-0.24[-0.55,0.07]
Qureshi 1998 (severe)	136	-4.5 (2.1)	135	-4.1 (2.2)		62.49%	-0.22[-0.46,0.02]
BI [pers comm]	246	-6.7 (0)	254	-6.4 (0)			Not estimable
Total ***	**461**		**473**			**100%**	**-0.23[-0.42,-0.04]**
Heterogeneity: Tau²=0; Chi²=0.01, df=1(P=0.92); I²=0%							
Test for overall effect: Z=2.36(P=0.02)							



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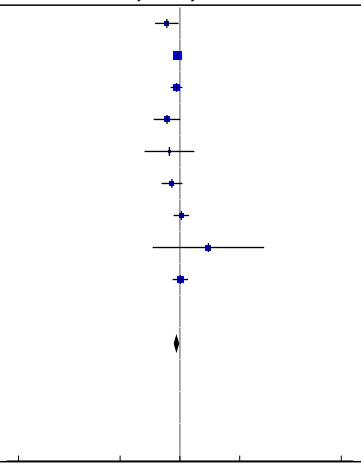
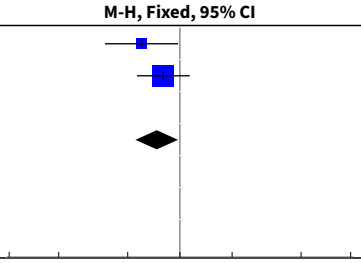
Analysis 1.13. Comparison 1 Anticholinergic and beta$_2$-agonists versus beta$_2$-agonists alone (all protocols), Outcome 13 Need for repeat bronchodilator treatment after standard protocol prior to disposition.

Study or subgroup	Anticholinergic + SABA n/N	SABA n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Zorc 1999 (severe)	11/22	24/29		7.24%	0.6[0.39,0.95]
Peterson 1996	68/82	73/81		25.68%	0.92[0.81,1.04]
Zorc 1999 (moderate)	55/97	62/96		21.79%	0.88[0.7,1.1]
Zorc 1999 (mild)	16/60	25/57		8.96%	0.61[0.36,1.01]
Benito Fernandez 2000	6/51	9/51		3.15%	0.67[0.26,1.74]
Schuh 1995 (multiple)	21/40	15/21		6.88%	0.74[0.49,1.1]
Schuh 1995 (single)	31/39	15/20		6.93%	1.06[0.79,1.43]
Cook 1985	3/15	1/15		0.35%	3[0.35,25.68]
Ducharme 1998	58/156	52/142		19.03%	1.02[0.75,1.37]
Total (95% CI)	**562**	**512**		**100%**	**0.87[0.79,0.97]**
Total events: 269 (Anticholinergic + SABA), 276 (SABA)					
Heterogeneity: Tau^2=0; Chi^2=10.06, df=8(P=0.26); I^2=20.47%					
Test for overall effect: Z=2.45(P=0.01)					



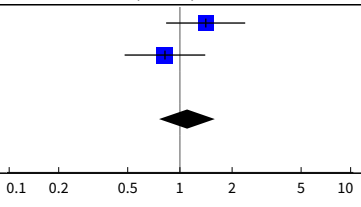
Analysis 1.14. Comparison 1 Anticholinergic and beta$_2$-agonists versus beta$_2$-agonists alone (all protocols), Outcome 14 O_2 saturation < 95% at 60 minutes (± 15 minutes).

Study or subgroup	Anticholinergic + SABA n/N	SABA n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Schuh 1995	22/79	19/41		33.55%	0.6[0.37,0.98]
Ducharme 1998	42/156	47/140		66.45%	0.8[0.57,1.14]
Total (95% CI)	**235**	**181**		**100%**	**0.73[0.55,0.97]**
Total events: 64 (Anticholinergic + SABA), 66 (SABA)					
Heterogeneity: Tau^2=0; Chi^2=0.9, df=1(P=0.34); I^2=0%					
Test for overall effect: Z=2.14(P=0.03)					



Analysis 1.15. Comparison 1 Anticholinergic and beta$_2$-agonists versus beta$_2$-agonists alone (all protocols), Outcome 15 O_2 saturation < 95% at 120 minutes (± 30 minutes).

Study or subgroup	Anticholinergic + SABA n/N	SABA n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ducharme 1998	24/58	15/51		47.67%	1.41[0.83,2.38]
Schuh 1995	14/37	18/39		52.33%	0.82[0.48,1.4]
Total (95% CI)	**95**	**90**		**100%**	**1.1[0.76,1.59]**
Total events: 38 (Anticholinergic + SABA), 33 (SABA)					



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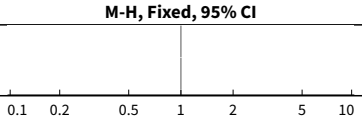
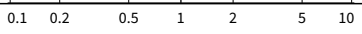
Study or subgroup	Anticholinergic + SABA n/N	SABA n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=2.01, df=1(P=0.16); I²=50.24%					
Test for overall effect: Z=0.5(P=0.62)					



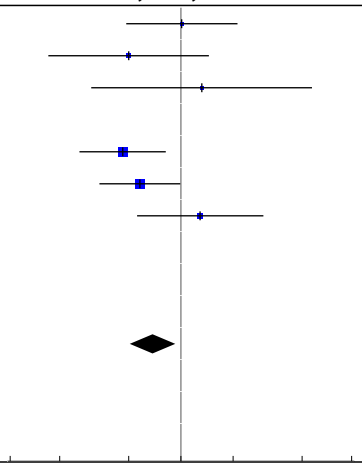
Analysis 1.16. Comparison 1 Anticholinergic and beta$_2$-agonists versus beta$_2$-agonists alone (all protocols), Outcome 16 Need for corticosteroids in emergency department prior to disposition.

Study or subgroup	Anticholinergic + SABA n/N	SABA n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ducharme 1998	86/156	85/142		90.82%	0.92[0.76,1.12]
Calvo 1998	5/40	9/40		9.18%	0.56[0.2,1.51]
Total (95% CI)	**196**	**182**		**100%**	**0.89[0.73,1.08]**
Total events: 91 (Anticholinergic + SABA), 94 (SABA)					
Heterogeneity: Tau²=0; Chi²=0.98, df=1(P=0.32); I²=0%					
Test for overall effect: Z=1.2(P=0.23)					



Analysis 1.17. Comparison 1 Anticholinergic and beta$_2$-agonists versus beta$_2$-agonists alone (all protocols), Outcome 17 Tremor.

Study or subgroup	Anticholinergic + SABA n/N	SABA n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Reisman 1988	6/11	7/13		11.28%	1.01[0.48,2.12]
Sharma 2004	4/25	8/25		14.07%	0.5[0.17,1.45]
Peterson 1996	4/82	3/81		5.31%	1.32[0.3,5.7]
Watson 1988	0/16	0/15			Not estimable
Schuh 1995 (multiple)	12/40	13/20		30.48%	0.46[0.26,0.82]
Schuh 1995 (single)	14/39	13/21		29.72%	0.58[0.34,0.99]
Beck 1985	7/13	5/12		9.14%	1.29[0.56,2.99]
Calvo 1998	0/40	0/40			Not estimable
Guill 1987	0/16	0/15			Not estimable
Total (95% CI)	**282**	**242**		**100%**	**0.69[0.51,0.93]**
Total events: 47 (Anticholinergic + SABA), 49 (SABA)					
Heterogeneity: Tau²=0; Chi²=6.59, df=5(P=0.25); I²=24.09%					
Test for overall effect: Z=2.45(P=0.01)					



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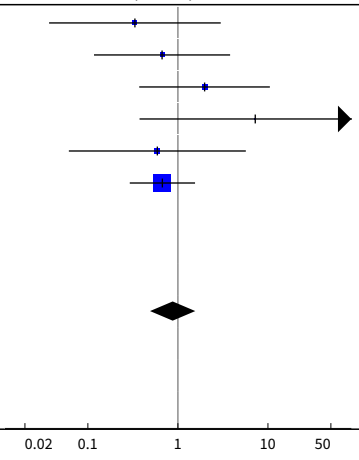
Analysis 1.18. Comparison 1 Anticholinergic and beta$_2$-agonists versus beta$_2$-agonists alone (all protocols), Outcome 18 Vomiting.

Study or subgroup	Anticholinergic + SABA n/N	SABA n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Sharma 2004	1/25	3/25		13.05%	0.33[0.04,2.99]
Qureshi 1997	2/45	3/45		13.05%	0.67[0.12,3.8]
Peterson 1996	4/82	2/81		8.75%	1.98[0.37,10.49]
BI [pers comm]	3/246	0/254		2.14%	7.23[0.38,139.18]
Reisman 1988	1/11	2/13		7.97%	0.59[0.06,5.68]
Ducharme 1998	9/154	12/138		55.04%	0.67[0.29,1.55]
Calvo 1998	0/40	0/40			Not estimable
Guill 1987	0/16	0/15			Not estimable
Total (95% CI)	**619**	**611**		**100%**	**0.88[0.49,1.56]**

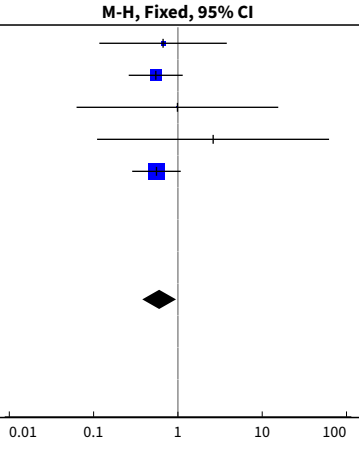
Total events: 20 (Anticholinergic + SABA), 22 (SABA)
Heterogeneity: Tau^2=0; Chi^2=4.21, df=5(P=0.52); I^2=0%
Test for overall effect: Z=0.45(P=0.65)



Analysis 1.19. Comparison 1 Anticholinergic and beta$_2$-agonists versus beta$_2$-agonists alone (all protocols), Outcome 19 Nausea.

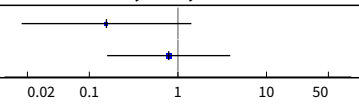
Study or subgroup	Anticholinergic + SABA n/N	SABA n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Qureshi 1997	2/45	3/45		7.39%	0.67[0.12,3.8]
Schuh 1995	8/40	15/41		36.47%	0.55[0.26,1.14]
Peterson 1996	1/82	1/81		2.48%	0.99[0.06,15.53]
Watanasomsiri 2006	1/38	0/33		1.32%	2.62[0.11,62.1]
Ducharme 1998	12/122	21/119		52.35%	0.56[0.29,1.08]
Calvo 1998	0/40	0/40			Not estimable
Guill 1987	0/16	0/15			Not estimable
Total (95% CI)	**383**	**374**		**100%**	**0.6[0.38,0.95]**

Total events: 24 (Anticholinergic + SABA), 40 (SABA)
Heterogeneity: Tau^2=0; Chi^2=1.08, df=4(P=0.9); I^2=0%
Test for overall effect: Z=2.18(P=0.03)



Analysis 1.20. Comparison 1 Anticholinergic and beta$_2$-agonists versus beta$_2$-agonists alone (all protocols), Outcome 20 Relapse.

Study or subgroup	Anticholinergic + SABA n/N	SABA n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Schuh 1995	1/47	3/22		12.29%	0.16[0.02,1.42]
Reisman 1988	2/11	3/13		8.27%	0.79[0.16,3.9]



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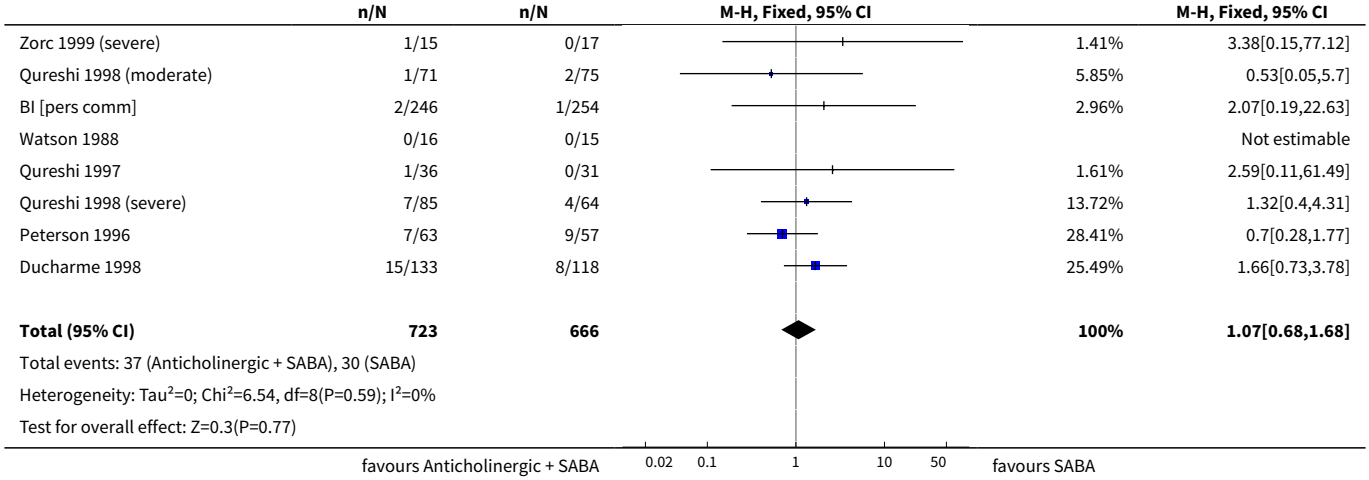

ADDITIONAL TABLES

Table 1. Study treatments

Protocol	Study	Age range (years)	Delivery device	Dose of ipratropium bromide	Number of doses	Total dose delivered
Single dose	Beck 1985	6-17.5	Nebulized	250 mcg	1	250 mcg
	Chakraborti 2006	5-15	MDI and spacer	80 mcg	1	80 mcg
	Cook 1985	12-18	Nebulized	1-2 mL of 0.025% solution	1	1-2 mL of 0.025% solution
	Ducharme 1998	3-17	Nebulized	250 mcg	1	250 mcg
	Phanichyakam 1990	4-14	MDI and spacer	40 mcg	1	40 mcg
	Schuh 1995 (single) (single dose)	5-17	Nebulized	250 mcg	1	250 mcg
Multiple fixed-dose protocol	Benito Fernandez 2000	5 months to 16 years	Nebulized	250 mcg	2	500 mcg
	BI [pers comm]	2-10	Nebulized	500 mcg	3	1500 mcg
	Iramain 2011	2-18	Nebulized	500 mcg children over 20 kg 250 mcg children under 20 kg	6	3000 mcg or 1500 mcg
	Peterson 1996	5-12	Nebulized	250 mcg	2	500 mcg
	Qureshi 1997	6-18	Nebulized	500 mcg	2	1000 mcg

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Table 1. Study treatments *(Continued)*

	Qureshi 1998 (moderate)	2-18	Nebulized	500 mcg	2	1000 mcg
	Qureshi 1998 (severe)	2-18	Nebulized	500 mcg	2	1000 mcg
	Reisman 1988	5-15	Nebulized	250 mcg	3	750 mcg
	Schuh 1995 (multiple dose)	5-17	Nebulized	250 mcg	3	750 mcg
	Sharma 2004	6-14	Nebulized	250 mcg	3	750 mcg
	Sienra Monge 2000	8-15	MDI and spacer	120 mcg	2	240 mcg
	Watanasomsiri 2006	3-15	Nebulized	250 mcg	3	750 mcg
	Watson 1988	6-17	Nebulized	250 mcg	2	500 mcg
	Zorc 1999 (mild)	1-17	Nebulized	500 mcg	2	1000 mcg
	Zorc 1999 (moderate)	1-17	Nebulized	500 mcg	2	1000 mcg
	Zorc 1999 (severe)	1-17	Nebulized	500 mcg	2	1000 mcg
Multiple flexible-**dose protocol**	Calvo 1998	5-14	MDI and spacer	20 mcg	Max 7	140 mcg (max)
	Guill 1987	13 months to 13 years	Nebulized	0.05-0.1 mg/kg	Max 3	0.15-0.3 mg/kg (max)

Max: maximum; MDI: metered-dose inhaler.

Table 2. Severity based on review author assessment of trial report

Study	MEAN FEV_1/PEFR (inclusion criteria)	MEAN score	Trial report description of severity	Review authors severity classification	Age
Beck 1995	FEV 30-31% (eligibility: FEV_1 < 50% pred)	Not reported	Severe	Severe	6 years-upper range not reported
Benito-Fernandez 2000	Mean PEF: 45% predicted	4.5 on a 5-point score	Moderate to severe	Severe	5 months to 16 years
BI (pers comm)	Unclear if measured	severity score of 13 (unknown scale)	Severe	Severe	2-10 years
Calvo (1998)	PEF = 69-71% (excluded if PEF > 80% pred.)	12-point TAL score: 5.6-6 (moderate)	Moderate	Moderate	5-14 years
Chakraborti (2006)	FEV_1 69-71 ± 37% (S+IB) and 57 ± 21% (S alone)	10-point clinical asthma score 1.83 (S+IB) vs. 2.07 (S alone)	Mild and moderate	Mild and moderate	5-15 years

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Table 2. Severity based on review author assessment of trial report *(Continued)*

Ducharme (1998)	Children requiring continuous nebulizations of salbutamol were excluded		Mild and moderate	Mild and moderate	3-7 years
Iramain (2011)	FEV_1 60-64%/PEF 62-60%	15-point pulmonary score: 12.3	Moderate and severe	Moderate and severe	2-18 years
Pederson (1996)	Mean not reported (eligibility FEV_1 < 70% pred.)	Not reported	Not reported	Moderate and severe	5-12 years
Qureshi (1997)	Mean FEV_1 and PEF at baseline 37% and 34% (eligibility FEV_1 < 50% pred.)	Not reported	Severe	Severe	6-18 years
Qureshi (1998) (sev)	Subgroup data provided by author: FEV_1 34% (eligibility FEV_1 < 50% pred.)	12-15 on 15-point asthma score)	Severe	Severe	2-18 years
Qureshi (1998) (mod)	Subgroup data provided by author: FEV_1 55% (eligibility: 50% < FEV_1 < 70% pred.)	8-11 on a 15-point Clinical score	Moderate	Moderate	2-18 years
Reisman (1998)	FEV_1 33-40% (eligibility; FEV_1 < 55% pred.)	-	Severe	Severe	5-15 years
Schuh (1995)	mean FEV_1-34% (eligibility; FEV_1 < 50% pred.)	wheezing score 2.2-2.5 on max of 3	Severe	Severe	5-17 years
Sharma (2004)	PEF 35% pred. (excluded PEF < 30% pred. and signs of impending respiratory disease	Wheezing score 2.5 to 2.6 (max = 3)	Moderate	Severe	6-14 years
Sienra monge (2000)	FEV_1: 1 L	not reported	Moderate to severe	Unrated	8-15 years
Watson (1988)	Mean FEV_1 not reported (eligibility FEV_1: 30-70% pred.)	5.7-6 on a scale of 0 to 12	Moderate and severe	Moderate and severe	6-17 years
Watanasomsiri (2006)	Mean % pred. PEFR at baseline 27-30% in the subset of people cooperating with the forced expiratory technique)(PEFR was not an inclusion criteria) no exclusion or inclusion based on severity	6.42 on a scale of 0 to 12	Proportion of moderate asthma: 73% and of severe asthma: 27%	Moderate and severe	3-15 years
Zorc (1999)	Subgroups data obtained from authors	Not reported	-	3 strata (mild, moderate and severe)	1-17 years

FEV_1: forced expiratory volume in one second; IB: ipratropium bromide; max: maximum; PEF: peak expiratory flow; PEFR: peak expiratory flow rate; pred.: predicted; S: salbutamol; y.o.: years old.

Table 3. Studies grouped by control group event rate as a proxy for severity

Protocol	Study	Admission rate (control group)	Baseline population spirometry characteristics	Admission rate - ranking

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Table 3. Studies grouped by control group event rate as a proxy for severity *(Continued)*

			(where available)	
Multiple fixed-dose protocol	Benito Fernandez 2000	0.53	PEFR (%) mean 44.8	High
	Qureshi 1998 (severe)	0.52	PEFR < 50% predicted	High
	Schuh 1995 (multiple)	0.46	FEV_1 < 50% predicted	High
	Qureshi 1997	0.45	PEFR < 50% predicted	High
	Iramain 2011	0.43	PEF or FEV_1 < 60% predicted	High
	Zorc 1999 (severe)	0.41	Not reported	Medium
	Peterson 1996	0.30	FEV_1 < 70% predicted	Medium
	Zorc 1999 (moderate)	0.26	Not reported	Medium
	Reisman 1988	0.23	FEV_1 < 55% predicted	Medium
	Sharma 2004	0.16	% predicted PEFR 34.4% (mean)	Medium
	Qureshi 1998 (moderate)	0.09	PEFR < 70% predicted	Low
	Watanasomsiri 2006	0.09	% PEFR 29.2	Low
	BI [pers comm]	0.09	Not reported	Low
	Zorc 1999 (mild)	0.07	Not reported	Low
	Watson 1988	0.00	Not reported	Low
Single-dose protocol	Schuh 1995 (single)	0.46	FEV_1 < 50% predicted	High
	Ducharme 1998	0.17	Respiratory resistance	Medium
	Chakraborti 2006	0.00	FEV_1 < 80%	Low

FEV_1: forced expiratory volume in one second; PEF: peak expiratory flow; PEFR: peak expiratory flow rate.

Table 4. Number needed to treat for hospital admissions grouped by severity tertile

Risk tertile	Weighted control group risk	Risk ratio (95% CI)	Corresponding treatment group risk (95% CI)	NNTB (95% CI)
Low	8.0%	0.91 (0.59 to 1.42)	7% (4 to 11)	139 (not significant)
Medium	24.1%	0.75 (0.57 to 0.99)	18% (14 to 24)	17 (10 to 415)
High	48.7%	0.68 (0.56 to 0.82)	33% (27 to 40)	7 (5 to 12)

Comparing the control group weighted risk against the treatment group's risk it can be seen that the NNTB in the high risk group was 7 versus 13 in the medium-risk group and 131 in the low-risk group.
CI: confidence interval; NNTB: number need to treat for an additional beneficial effect.

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APPENDICES

Appendix 1. Archive of search results for review

Issue 3, 2000

Forty studies were reviewed in full text for possible inclusion; 37 studies were identified by the literature search and bibliographies and three studies were identified by contact with trialists. A total of 13 randomised controlled trials were selected for inclusion.

WHAT'S NEW

Date	Event	Description
4 September 2013	Amended	Typo in BG affiliation amended

HISTORY

Protocol first published: Issue 1, 1996
Review first published: Issue 2, 1997

Date	Event	Description
18 April 2012	New citation required and conclusions have changed	Seven new studies added (Benito Fernandez 2000; Chakraborti 2006; Iramain 2011; Sharma 2004; Sienra Monge 2000; Watanasomsiri 2006) making a total of 20 studies including 2697 children; methods for assessing risk of bias updated; summary of findings table added; conclusions changed.
18 April 2012	New search has been performed	Literature search re-run
22 July 2008	Amended	Converted to new review format.
25 April 2000	New citation required and conclusions have changed	Three new trials were included in this update; two pertaining to the multiple dose - fixed protocol (Qhreshi, 1998; Zorc, 1999) and one pertaining to the multiple dose - flexible protocol (Calvo, 1998); one previously unpublished trial (Ducharme, 1995) was published and is hereafter referred to as Ducharme, 1998. The addition of these new trials confirmed previous findings about the efficacy of intensive anticholinergics and beta2-agonist inhalations in acute severe pediatric asthma. It raised the possibility that intensive therapy may have some benefits for children with moderate exacerbations by reducing the number of inhalations required after the fixed protocol. Despite a new trial testing the multiple-dose flexible protocol, the evidence is still insufficient to conclude about the benefits of the systematic addition of anticholinergics to every beta2-agonist inhalation, irrespective of disease severity. No new trial was added to the single dose protocol, which remains unchanged.

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CONTRIBUTIONS OF AUTHORS

BG: drafted the current version of the update.

FMD: designed and supervised the conduct of the original review, reviewed, interpreted and approved the updated review.

DECLARATIONS OF INTEREST

Francine Ducharme has received travel support, research funds and fees for speaking from Novartis, Taketa (formally Nycomed) and Merck Frosst Inc and served on an advisory board for Novartis.

SOURCES OF SUPPORT

Internal sources

- NHS Research and Development, UK.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We updated the following methods in the present update (2013)

- Removed presentation of subgroup by co-treatment with corticosteroids and applied this and additional subgroups to the primary outcome only.
- Combined all comparisons originally presented by protocol (single dose, multiple fixed dose and multiple flexible doses) into a single comparison.
- We updated the 'Risk of bias' assessment from Jadad to the 'Risk of bias' tables currently recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Inhalation; Adrenergic beta-2 Receptor Agonists [administration & dosage] [*therapeutic use]; Asthma [*drug therapy]; Atropine [administration & dosage] [therapeutic use]; Cholinergic Antagonists [administration & dosage] [*therapeutic use]; Disease Progression; Drug Therapy, Combination [methods]; Hospitalization [statistics & numerical data]; Ipratropium [administration & dosage] [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adolescent; Child; Child, Preschool; Humans; Infant

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